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(54) **N-ACYLSULFONAMIDE APOPTOSIS PROMOTERS**

N-ACYLSULFONAMIDE ALS DIE APOPTOSE FÖRDERNDE VERBINDUNGEN

PROMOTEURS DE L'APOPTOSE CONTENANT N-ACYLSULFONAMIDE

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- **THOMAS H. CORBETT ET AL.: "Discovery and preclinical antitumor efficacy evaluations of LY32262 and LY33169" INVESTIGATIONAL NEW DRUGS, vol. 21, February 2003 (2003-02), pages 33-45, XP002326753**

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Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

Description

FIELD OF THE INVENTION

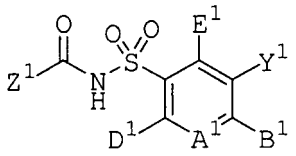
[0001] This invention pertains to compounds which inhibit the activity of anti-apoptotic protein family members, compositions containing the compounds, and uses of the compounds for preparing medicaments for treating diseases during which are expressed of one or more than one of an anti-apoptotic protein family member.

BACKGROUND OF THE INVENTION

[0002] Anti-apoptotic protein family members are associated with a number of diseases. There is therefore an existing need in the therapeutic arts for compounds which inhibit the activity of one of more than one of an anti-apoptotic protein family member.
WO 02/24636 discloses N-Benzoyl arylsulfonamides that are BC1-X_1 inhibitors and are useful for promoting apoptosis. Also disclosed are BC1-X_1 inhibiting compositions and methods of promoting apoptosis in a mammal.
WO 03/040107 discloses substituted imidazole derivatives which have been found to suppress appetite and induce weight loss. WO 03/040107 also provides methods for synthesis of the compounds, pharmaceutical compositions comprising the compounds, and methods of using such compositions for inducing weight loss and treating obesity and obesity-related disorders. WO 02/098848 discloses certain benzoylsulfonamides and sulfonylbenzamidines for use as antitumor agents.
Thomas H. Corbett et al. in "Discovery and preclinical antitumor efficacy evaluations of LY32262 and LY33169" Investigational new Drugs, Vol. 21, February 2003 (2003-02), pages 33-45, XP002326753, disclose the discovery of a new antitumor agent (LY32262) (N-[2,4-dichlorobenzoyl]phenylsulfonamide) and of a close analog thereof (LY33169).

SUMMARY OF THE INVENTION

[0003] One embodiment of this invention, therefore, pertains to compounds or therapeutically acceptable salts thereof, which are useful as inhibitors of one or more than one anti-apoptotic protein family member, the compounds having formula (I)



(I),

wherein A^1 is $C(A^2)$;

A^2 is H, F, CN, C (O) OH, C (O) NH_2 or C (O) OCH_3;
B^1 is R^1, OR^1, NHR^1, $N(R^1)_2$ or $NR^1C(O)N(R^1)_2$;
D^1 is H, F, Cl or CF_3;
E^1 is H, F or Cl;
Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2, $C(O)NH_2$, or
B^1 and Y_1, together with the atoms to which they are attached, are imidazole or triazole;
R^1 is phenyl, pyrrolyl, cyclopentyl, cyclohexyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl or R^5;
R^5 is C_1-alkyl, C_2-alkyl, C_3-alkyl, C_4-alkyl, C_5-alkyl or C_6-alkyl, each of which is unsubstituted or substituted with one or two or three independently selected
C_4-spiroalkyl, C_5-spiroalkyl, R^7, OR^7, SR^7, SO_2R^7, NHR^7, $N(R^7)_2$, C (O) R^7, C (O) NH_2, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, $NHC(O)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, OH, C(O)OH or NH_2 substituents;
R^7 is phenyl, furanyl, imidazolyl, pyridinyl, tetrazolyl, thiazolyl, thienyl, 1,3-benzoxazolyl, 1,3-benzodioxolyl, 1,3-benzothiazole, cyclopropyl, cyclobutyl, cyclohexyl, azetidinyl, morpholinyl, piperazinyl, piperidinyl, thiomorpholinyl, thiomorpholinyl sulfone 7-azabicyclo[2.2.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, 4,5-dihydro-1H-imidazolyl 2-oxa-5-azabicyclo[2.2.1]heptanyl, 1,4,5,6-tetrahydropyrimidinyl or R^{11};
R^{11} is C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, $N(R^{12})_2$, $C(O)N(R^{12})_2$, OH, C(O)OH, NH_2, CF_3, F, Cl, Br or I substituents;

R^{12} is 1,3-benzodioxolyl, pyridinyl, morpholinyl or C_1-alkyl;
Z^1 is phenyl or pyridinyl, each of which is substituted with cyclohexenyl, piperazinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl or octahydropyrrolo[3,4-c]pyrrolyl, each of which is substituted with CH_2R^{37}, $C(C_2$-spiroalkyl) (R^{37}) or $C(O)R^{37}$;
R^{37} is phenyl, naphthyl, imidazolyl, pyrazolyl, pyridinyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl or 3,6-dihydro-2H-pyranyl, each of which is substituted with R^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$ or SR^{41};
R^{41} is phenyl, naphthyl, cyclohexyl, morpholinyl, piperidinyl, thienyl, pyridinyl, quinolinyl, benzofuranyl, 1,3-benzodioxolyl, isoindolinyl, 1,3-oxazolidin-2-onyl or R^{45};
R^{45} is C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is substituted with phenyl;
wherein the moieties represented by B^1 and Y^1 together are substituted with C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is substituted with one or two independently selected SR^{55} or $N(R^{55})_2$ substituents, wherein R^{55} is independently selected phenyl or C_1-alkyl;
the moieties represented by R^1 are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, SR^{50}, SO_2R^{50}, $CO(O)R^{50}$ or OCF_3 substituents, wherein R^{50} is phenyl, C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl;
the moieties represented by R^7 are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, $C(O)NHSO_2R^{50}$, $CO(O)R^{50}$, $C(O)R^{50}$, C(O)OH, C (O) NHOH, OH, NH_2, F, Cl, Br or I substituents, wherein R^{50} is phenyl, tetrazolyl or R^{54}, wherein R^{54} is C_1-alkyl, C_2-alkyl or C_3-alkyl, each of which is unsubstituted or substituted with phenyl;
the phenyl and pyridinyl moieties of Z^1 are further unsubstituted or substituted with one or two independently selected F, Br, Cl or I substituents;
the cyclohexenyl, piperazinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl and octahydropyrrolo[3,4-c]pyrrolyl moieties of Z^1 are further unsubstituted or substituted with OR^{54}, wherein R^{54} is C_1-alkyl or C_2-alkyl, each of which is unsubstituted or substituted with $N(C_1$-alkyl$)_2$, morpholinyl, piperidinyl or piperidinyl;
the moieties represented by R^{37} are further unsubstituted or substituted with one or two independently selected C_1-alkyl, F, Br, Cl or I substituents; and
the moieties represented by R^{41} are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, SR^{50}, $N(R^{50})_2$, SO_2R^{50}, CN, CF_3, F, Cl, Br or I substituents, wherein R^{50} is phenyl or R^{54}, wherein R^{54} is C_1-alkyl, C_2-alkyl or C_3-alkyl, each of which is unsubstituted or substituted with $N(C_1$-alkyl$)_2$ or morpholinyl.

[0004] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoro-ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-l-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(1,3-benzodioxol-5-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(benzofuran-2-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-bromophenyl)phenylmethyl)piperazin-1-yl)phenylcarbo-

nyl, 4-(4-(2-(4-chlorophenyl)cyclohept-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclooct-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)-piperazin-1-yl)phenylcarbonyl, 4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylmethyl, 4-(4-(2-(4-chlorophenyl)naphth-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)pyridin-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(4-chlorophenyl)pyridin-4-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)pyridin-5-yl)methyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylcycloprop-1-yl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-chlorophenyl)phenylmethyl)cyclohex-1-en-1-yl)phenylcarbonyl.

[0005] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)-pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethyl-pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethyl-pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or C (O) NH_2; and Z^1 is 4-(5-(2-(4-chlorophenyl)phenylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2 (1H)-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)-3,5-difluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-2-fluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-3-fluorophenylcarbonyl, 2-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-5-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)piperidin-4-yl)phenylcarbonyl, 5-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)pyridin-2-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(cyclohex-1-ylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl4-(4-(2-cyclohex-1-ylphenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-cyanophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-difluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(1,3-dihydro-2H-isoindol-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(1,1-dimethylethoxycarbonylamino)phenyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-(2-(dimethylamino)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(3-(dimethylamino)phenyl)piperazin-1-yl)phenylcarbonyl.

[0006] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino,

(1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)-pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethyl-pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl) propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(2-(4-(dimethylamino)phenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(dimethylamino)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)-3-fluorophenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(isopropylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(isopropylsulfanyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-('4-methoxyphenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-methoxy-4-(2-(pyridin-3-yl)phenylmethyl)piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methyl-4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(methylsulfonyl)phenyl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfonylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-((2-(4-methylsulfonylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl.

[0007] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or C (O) NH_2; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)-pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethyl-pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)pro-

pylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(5-methylthien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methylsulfanylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylmethyl)piperazin-1-yl)-phenylcarbonyl, 4-(4-(2-(4-(2-(morpholin-1-yl)ethoxy)-phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(morpholin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-2-yl)phenylmethyl)-piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-phenoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl) phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-((phenylmethyl)amino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(dimethylamino)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-((2-(phenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(morpholin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(phenyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(piperidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl.

[0008] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and 2^1 is 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-((2-(phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(piperidin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(pyrid-3-yl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-3-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-8-yl-phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)-4-methoxypiperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-trifluoromethoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-trifluoromethylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl.

[0009] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phe-

nyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-l-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(1,3-benzodioxol-5-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(benzofuran-2-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-bromophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohept-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclooct-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-l-yl)phenylcarbonyl, 4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylmethyl, 4-(4-(2-(4-chlorophenyl)naphth-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)pyridin-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(4-chlorophenyl)pyridin-4-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)pyridin-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylcycloprop-1-yl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-chlorophenyl)phenylmethyl)cyclohex-1-en-1-yl)phenylcarbonyl.

[0010] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)-pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethyl-pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or C (O) NH_2; and Z^1 is 4-(5-(2-(4-chlorophenyl)phenylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)-3,5-difluorophenylcarbonyl, 4-(4-(2-(4-chlorophe-

nyl)phenylmethyl)piperazin-1-yl)-2-fluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-3-fluorophenylcarbonyl, 2-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-5-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)piperidin-4-yl)phenylcarbonyl, 5-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)pyridin-2-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(cyclohex-1-ylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl4-(4-(2-cyclohex-1-ylphenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-cyanophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-difluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(1,3-dihydro-2H-isoindol-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(1,1-dimethylethoxycarbonylamino)phenyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-(2-(dimethylamino)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(3-(dimethylamino)phenyl)piperazin-1-yl)phenylcarbonyl.

[0011] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or C (O) NH_2; and Z^1 is 4- (2-(4-(dimethylamino)phenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(dimethylamino)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)-3-fluorophenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(isopropylamino)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(isopropylsulfanyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-methoxy-4-(2-(pyridin-3-yl)phenylmethyl)piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methyl-4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(methylsulfonyl)-phenyl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfonylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-((2-(4-methylsulfonylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl.

[0012] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino,

(1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(5-methylthien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methylsulfanylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylmethyl)piperazin-1-yl)-phenylcarbonyl, 4-(4-(2-(4-(2-(morpholin-1-yl)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(morpholin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-phenoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl) phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-((phenylmethyl)amino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(dimethylamino)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-((2-(phenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(morpholin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(phenyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(piperidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl.

[0013] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethylamino, (1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethylamino, (3R)-5-(N-((dimethylamino)methylcarbonyl)amino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propoxy, (1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((pyrimidin-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-3-oxo-1-((1,3-thiazol-2-yl)methyl)propylamino, (1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((1,1-dimethylethoxy)carbonylamino)-1-((phenylsulfanyl)methyl)pentylamino, 1-(1,1-dimethylethoxycarbonyl)piperidin-4-yloxy, 1,1-dimethyl-2-(phenylsulfonyl)ethylamino, (1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino, 1,1-dimethyl-2-(phenylsulfanyl)ethyl, 4,4-dimethylpiperidin-1-yl, (1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethylamino, (1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, 1,1-dimethyl-2-(thien-2-ylsulfanyl)ethylamino, (1R)-3-(1,1-dioxothiomorpholin-4-yl)-l-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, 1-(ethoxycarbonyl)piperidin-4-yloxy, (1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is

4-(4-(2-(phenyl)phenylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-((2-(phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(piperidin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(pyrid-3-yl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-3-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-8-yl-phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)-4-methoxypiperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-trifluoromethoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-trifluoromethylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl.

[0014] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or C (O) NH_2; B^1 is (1R)-3-(4-(hydroxyaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, isopropylamino, (1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)-propylamino, (4-methoxycyclohex-1-yl)methyl)amino, (1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-(N-methyl-N-carboxymethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (methyl)(cyclohexyl)amino, (methyl)(cyclohexylmethyl)amino, (1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(N-methyl-N-(dimethylcarbonylmethyl))-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(1,2-diphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-((diphenylmethyl)amino)carbonyl)-N-methylamino, (2-methylfuran-3-yl)sulfanyl)(1,1-spirobutyl)ethylamino, (1R)-3-(N-methyl-N-(2-hydroxyethyl))amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(4-methoxyphenyl)amino)carbonyl)-N-methylamino, 1-methyl-4-(phenylsulfanyl)pyrrolidin-3-ylamino, (N-methyl-N-(4-methylphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(2-methylphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1-methylpiperidin-4-yloxy, (N-methyl-N-((S)-1-phenylethyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(4-methylpiperazin-4-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(morpholin-1-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(N,N-dimethylamino)amino)carbonyl)-N-methylamino, (1R)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1S)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((methylsulfonylamino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(4-(methylsulfonylaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, 2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethylamino, (N-methyl-N-(4-trifluoromethoxyphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)-propylamino, (1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methyl)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(1,3-benzodioxol-5-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(benzofuran-2-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-bromophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohept-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclooct-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylmethyl, 4-(4-(2-(4-chlorophenyl)naphth-3-ylmethyl)piperazin-1-yl)-phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)pyridin-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(4-chlorophenyl)pyridin-4-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)pyridin-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylcycloprop-1-yl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-chlorophenyl)phenylmethyl)cyclohex-1-en-1-yl)phenylcarbonyl.

[0015] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-(4-(hydroxyaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, isopropylamino, (1R)-3-(isopropylamino)-1-((phe-

nylsulfanyl)methyl)propylamino, (1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)-propylamino, (4-methoxycyclohex-1-yl)methyl)amino, (1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-(N-methyl-N-carboxymethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (methyl)(cyclohexyl)amino, (methyl)(cyclohexylmethyl)amino, (1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(N-methyl-N-(dimethylcarbonylmethyl))-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(1,2-diphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-((diphenylmethyl)amino)carbonyl)-N-methylamino, (2-methylfuran-3-yl)sulfanyl)-(1,1-spirobutyl)ethylamino, (1R)-3-(N-methyl-N-(2-hydroxyethyl))amino)-1-((phenylsulfanyl)methyl)propylamino, (lR)-3-(N-methyl-N-isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(4-methoxyphenyl)amino)carbonyl)-N-methylamino, 1-methyl-4-(phenylsulfanyl)pyrrolidin-3-ylamino, (N-methyl-N-(4-methylphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(2-methylphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1-methylpiperidin-4-yloxy, (N-methyl-N-((S)-1-phenylethyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(4-methylpiperazin-4-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(morpholin-1-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(N,N-dimethylamino))amino)carbonyl)-N-methylamino, (1R)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1S)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((methylsulfonylamino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(4-(methylsulfonylaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, 2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethylamino, (N-methyl-N-(4-trifluoromethoxyphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-3-oxo-l-((2-thienylsulfanyl)methyl)-propylamino, (1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methyl)phenyl)sulfanyl)methyl)propylamino, (lR)-3-(morpholin-4-yl)-1-((phenylsulfonyl)-methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(5-(2-(4-chlorophenyl)phenylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-3,5-difluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl),piperazin-1-yl)-2-fluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-3-fluorophenylcarbonyl, 2-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-5-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)piperidin-4-yl)phenylcarbonyl, 5-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-2-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(cyclohex-1-ylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl4-(4-(2-cyclohex-1-ylphenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-cyanophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-difluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(1,3-dihydro-2H-isoindol-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(1,1-dimethylethoxycarbonylamino)phenyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-(2-(dimethylamino)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(3-(dimethylamino)phenyl)piperazin-1-yl)phenylcarbonyl.

[0016] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-(4-(hydroxyaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, isopropylamino, (1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (4-methoxycyclohex-1-yl)methyl)amino, (1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-carboxymethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (methyl)(cyclohexyl)amino, (methyl)(cyclohexylmethyl)amino, (1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(N-methyl-N-(dimethylcarbonylmethyl))-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(1,2-diphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-((diphenylmethyl)amino)carbonyl)-N-methylamino, (2-methylfuran-3-yl)sulfanyl)-(1,1-spirobutyl)ethylamino, (1R)-3-(N-methyl-N-(2-hydroxyethyl))amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(4-methoxyphenyl)amino)carbonyl)-N-methylamino, 1-methyl-4-(phenylsulfanyl)pyrrolidin-3-ylamino, (N-methyl-N-(4-methylphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(2-methylphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1-methylpiperidin-4-yloxy, (N-methyl-N-((S)-1-phenylethyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(4-methylpiperazin-4-yl))amino)carbonyl)-N-

methylamino, (N-methyl-N-(1-phenyl-2-(morpholin-1-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(N,N-dimethylamino))amino)carbonyl)-N-methylamino, (1R)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1S)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((methylsulfonylamino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(4-(methylsulfonylaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethylamino, (N-methyl-N-(4-trifluoromethoxyphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methyl)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(2-(4-(dimethylamino)phenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(dimethylamino)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)-3-fluorophenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(isopropylamino)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(isopropylsulfanyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-methoxy-4-(2-(pyridin-3-yl)phenylmethyl)piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methyl-4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methylphenyl)phenylmethyl)-piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(methylsulfonyl)-phenyl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfonylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-((2-(4-methylsulfonylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl.

[0017] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-(4-(hydroxyaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, isopropylamino, (1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (4-methoxycyclohex-1-yl)methyl)amino, (1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-carboxymethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (methyl)(cyclohexyl)amino, (methyl)(cyclohexylmethyl)amino, (1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(N-methyl-N-(dimethylcarbonylmethyl))-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(1,2-diphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-((diphenylmethyl)amino)carbonyl)-N-methylamino, (2-methylfuran-3-yl)sulfanyl)-(1,1-spirobutyl)ethylamino, (1R)-3-(N-methyl-N-(2-hydroxyethyl))amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(4-methoxyphenyl)amino)carbonyl)-N-methylamino, 1-methyl-4-(phenylsulfanyl)pyrrolidin-3-ylamino, (N-methyl-N-(4-methylphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(2-methylphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1-methylpiperidin-4-yloxy, (N-methyl-N-((S)-1-phenylethyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(4-methylpiperazin-4-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(morpholin-1-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(N,N-dimethylamino))amino)carbonyl)-N-methylamino, (1R)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1S)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((methylsulfonylamino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(4-(methylsulfonylaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethylamino, (N-methyl-N-(4-trifluoromethoxyphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methyl)phenyl)sulfanyl)methylpropylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2

or $C(O)NH_2$; and Z^1 is 4-(4-(2-(5-methylthien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methylsulfanylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(2-(morpholin-1-yl)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(morpholin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-phenoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl) phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-((phenylmethyl)amino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(dimethylamino)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-((2-(phenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(morpholin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(phenyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(piperidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl.

[0018] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-(4-(hydroxyaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, isopropylamino, (1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)-propylamino, (4-methoxycyclohex-1-yl)methyl)amino, (1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-carboxymethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (methyl)(cyclohexyl)amino, (methyl)(cyclohexylmethyl)amino, (1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (3R)-3-(N-methyl-N-(dimethylcarbonylmethyl))-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(1,2-diphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-((diphenylmethyl)amino)carbonyl)-N-methylamino, (2-methylfuran-3-yl)sulfanyl)-(1,1-spirobutyl)ethylamino, (1R)-3-(N-methyl-N-(2-hydroxyethyl))amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(N-methyl-N-isopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (N-methyl-N-(4-methoxyphenyl)amino)carbonyl)-N-methylamino, 1-methyl-4-(phenylsulfanyl)pyrrolidin-3-ylamino, (N-methyl-N-(4-methylphenyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(2-methylphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 1-methylpiperidin-4-yloxy, (N-methyl-N-((S)-1-phenylethyl)amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(4-methylpiperazin-4-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(morpholin-1-yl))amino)carbonyl)-N-methylamino, (N-methyl-N-(1-phenyl-2-(N,N-dimethylamino))amino)carbonyl)-N-methylamino, (1R)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1S)-1-methyl-2-((phenylsulfanyl)methyl)ethylamino, (1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butylamino, (1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-5-((methylsulfonylamino)-1-((phenylsulfanyl)methyl)pentylamino, (1R)-3-(4-(methylsulfonylaminocarbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, 2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethylamino, (N-methyl-N-(4-trifluoromethoxyphenyl)amino)carbonyl)-N-methylamino, (1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((thien-2-ylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methoxy)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(methyl)phenyl)sulfanyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propylamino, (1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-((2-(phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(piperidin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(pyrid-3-yl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-3-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-8-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)-4-methoxypiperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-trifluoromethoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-trifluoromethylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl.

[0019] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclopropylamino)-1-((phenyl-

sulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfonylmethyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((pyrimidin-1-ylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-((1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-oxo-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-amino-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(methylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(morpholin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(2-(morpholin-1-yl)ethyl)-1-((phenylsulfanyl)methyl)propylamino, (2-phenoxyethyl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)methylamino, (4-phenyl-1,3-thiazol-2-ylsulfanyl)ethylamino, (1R,2S)-2-(phenylsulfanyl)cyclohex-1-ylamino, (1S,2R)-2-(phenylsulfanyl)cyclohex-1-ylamino, 2-(phenylsulfanyl)cyclopentylamino, 2-(phenylsulfanyl)ethoxy, 2-(phenylsulfanyl)ethylamino, 2-(phenylsulfonyl)ethylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(morpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, 4-(phenylsulfonyl)tetrahydrofuran-3-ylamino, 4-(phenylsulfanyl)tetrahydrofuran-3-ylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, (1S)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propylamino), (1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)3-((pyridin-2-ylmethyl)amino)propylamino, (1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethylamino, (3S,4R)-(phenylsulfanyl)pyrrolidin-4-ylamino, 2-(phenylsulfanyl)-1,1-spirobutylethylamino, 2-(phenylsulfanyl)-1,1-spiroethylethylamino, 2-(phenylsulfanyl)-1,1-spiropentylethylamino, piperidin-4-yloxy, (1-propylpiperidin-4-yl)methylamino, pyran-4-ylamino, 2-(pyridin-4-ylsulfanyl)ethylamino, 2-(pyrimidin-2-ylsulfanyl)ethylamino, 1,1-spirobutyl-2-(phenylsulfanyl)ethyl, 2-(thien-2-ylsulfanyl)ethylamino, sulfanylpyran-4-ylamino, (1R)-3-(2-(2H-tetrazol-3-yl)pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(3-(2H-tetrazol-3-yl)azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino or 2-(1,3-thiazol-2-ylsulfanyl)ethylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(1,3-benzodioxol-5-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(benzofuran-2-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-bromocyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-bromophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohept-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)cyclooct-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohex-1-en-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylmethyl, 4-(4-(2-(4-chlorophenyl)naphth-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)pyridin-3-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(4-chlorophenyl)pyridin-4-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((4-(4-chlorophenyl)pyridin-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylcycloprop-1-yl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-chlorophenyl)phenylmethyl)cyclohex-1-en-1-yl)phenylcarbonyl.

[0020] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfonylmethyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((pyrimidin-1-ylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-((1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-oxo-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-amino-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(methylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-oxo-3-(morpholin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(2-(morpholin-1-yl)ethyl)-1-((phenylsulfanyl)methyl)propylamino, (2-phenoxyethyl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)methylamino, (4-phenyl-1,3-thiazol-2-ylsulfanyl)ethylamino, (1R,2S)-2-(phenylsulfanyl)cyclohex-1-ylamino, (1S,2R)-2-(phenylsulfanyl)cyclohex-1-ylamino,

2-(phenylsulfanyl)cyclopentylamino, 2-(phenylsulfanyl)ethoxy, 2-(phenylsulfanyl)ethylamino, 2-(phenylsulfonyl)ethylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(morpholin-4-yl)propylamino, (IR)-l-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, 4-(phenylsulfonyl)tetrahydrofuran-3-ylamino, 4-(phenylsulfanyl)tetrahydrofuran-3-ylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)-amino)propylamino, (1S)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propylamino), (1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)3-((pyridin-2-ylmethyl)amino)propylamino, (1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethylamino, (3S,4R)-(phenylsulfanyl)pyrrolidin-4-ylamino, 2-(phenylsulfanyl)-1,1-spirobutylethylamino, 2-(phenylsulfanyl)-1,1-spiroethylethylamino, 2-(phenylsulfanyl)-1,1-spiropentylethylamino, piperidin-4-yloxy, (1-propylpiperidin-4-yl)methylamino, pyran-4-ylamino, 2-(pyridin-4-ylsulfanyl)ethylamino, 2-(pyrimidin-2-ylsulfanyl)ethylamino, 1,1-spirobutyl-2-(phenylsulfanyl)ethyl, 2-(thien-2-ylsulfanyl)ethylamino, sulfanylpyran-4-ylamino, (1R)-3-(2-(2H-tetrazol-3-yl)pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(3-(2H-tetrazol-3-yl)azetidin-1-yl)-1-((phenyl,sulfanyl)methyl)propylamino or 2-(1,3-thiazol-2-ylsulfanyl)ethylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(5-(2-(4-chlorophenyl)phenylmethyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)-piperazin-1-yl)-3,5-difluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-2-fluorophenylcarbonyl, 4-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)-3-fluorophenylcarbonyl, 2-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-5-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)piperidin-4-yl)phenylcarbonyl, 5-(4-(2-(4-chlorophenyl)phenylmethyl)piperazin-1-yl)pyridin-2-ylcarbonyl, 4-(1-(2-(4-chlorophenyl)phenylmethyl)-1,2,3,6-tetrahydropyridin-4-yl)phenylcarbonyl, 4-(4-(2-(cyclohex-1-ylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl4-(4-(2-cyclohex-1-ylphenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-cyanophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3,4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2,4-difluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(1,3-dihydro-2H-isoindol-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(1,1-dimethylethoxycarbonylamino)phenyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(4-(2-(dimethylamino)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(3-(dimethylamino)phenyl)piperazin-1-yl)phenylcarbonyl.

[0021] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-oxo-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfonylmethyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((pyrimidin-1-ylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-((1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)-propylamino, (1R)-3-oxo-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-amino-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(methylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(morpholin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(2-(morpholin-1-yl)ethyl)-1-((phenylsulfanyl)methyl)propylamino, (2-phenoxyethyl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)methylamino, (4-phenyl-1,3-thiazol-2-ylsulfanyl)ethylamino, (1R,2S)-2-(phenylsulfanyl)cyclohex-1-ylamino, (1S,2R)-2-(phenylsulfanyl)cyclohex-1-ylamino, 2-(phenylsulfanyl)cyclopentylamino, 2-(phenylsulfanyl)ethoxy, 2-(phenylsulfanyl)ethylamino, 2-(phenylsulfonyl)ethylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(morpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, 4-(phenylsulfonyl)tetrahydrofuran-3-ylamino, 4-(phenylsulfanyl)tetrahydrofuran-3-ylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, (1S)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propylamino), (1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-2-ylmethyl)amino)propylamino, (1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethylamino, (3S,4R)-(phenylsulfanyl)pyrrolidin-4-ylamino,

2-(phenylsulfanyl)-1,1-spirobutylethylamino, 2-(phenylsulfanyl)-1,1-spiroethylethylamino, 2-(phenylsulfanyl)-1,1-spiropentylethylamino, piperidin-4-yloxy, (1-propylpiperidin-4-yl)methylamino, pyran-4-ylamino, 2-(pyridin-4-ylsulfanyl)ethylamino, 2-(pyrimidin-2-ylsulfanyl)ethylamino, 1,1-spirobutyl-2-(phenylsulfanyl)ethyl, 2-(thien-2-ylsulfanyl)ethylamino, sulfanylpyran-4-ylamino, (1R)-3-(2-(2H-tetrazol-3-yl)pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(3-(2H-tetrazol-3-yl)azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino or 2-(1,3-thiazol-2-ylsulfanyl)ethylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(2-(4-(dimethylamino)phenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(dimethylamino)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)-3-fluorophenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-fluorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-(isopropylamino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(isopropylsulfanyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)cyclopent-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(3-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-methoxy-4-(2-(pyridin-3-yl)phenylmethyl)piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methyl-4-dichlorophenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(2-methylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(methylsulfonyl)phenyl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfonylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-((2-(4-methylsulfonylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl.

[0022] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfonylmethyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((pyrimidin-1-ylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-((1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-amino-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(methylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(morpholin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(2-(morpholin-1-yl)ethyl)-1-((phenylsulfanyl)methyl)propylamino, (2-phenoxyethyl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)methylamino, (4-phenyl-1,3-thiazol-2-ylsulfanyl)ethylamino, (1R,2S)-2-(phenylsulfanyl)cyclohex-1-ylamino, (1S,2R)-2-(phenylsulfanyl)cyclohex-1-ylamino, 2-(phenylsulfanyl)cyclopentylamino, 2-(phenylsulfanyl)ethoxy, 2-(phenylsulfanyl)ethylamino, 2-(phenylsulfonyl)ethylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(morpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, 4-(phenylsulfonyl)tetrahydrofuran-3-ylamino, 4-(phenylsulfanyl)tetrahydrofuran-3-ylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)-amino)propylamino, (1S)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propylamino), (1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-2-ylmethyl)amino)propylamino, (1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethylamino, (3S,4R)-(phenylsulfanyl)pyrrolidin-4-ylamino, 2-(phenylsulfanyl)-1,1-spirobutylethylamino, 2-(phenylsulfanyl)-1,1-spiroethylethylamino, 2-(phenylsulfanyl)-1,1-spiropentylethylamino, piperidin-4-yloxy, (1-propyl-piperidin-4-yl)methylamino, pyran-4-ylamino, 2-(pyridin-4-ylsulfanyl)ethylamino, 2-(pyrimidin-2-ylsulfanyl)ethylamino, 1,1-spirobutyl-2-(phenylsulfanyl)ethyl, 2-(thien-2-ylsulfanyl)ethylamino, sulfanylpyran-4-ylamino, (1R)-3-(2-(2H-tetrazol-3-yl)pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(3-(2H-tetrazol-3-yl)azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino or 2-(1,3-thiazol-2-ylsulfanyl)ethylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$; and Z^1 is 4-(4-(2-(5-methylthien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)cyclohex-1-en-1-ylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylcarbonyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((2-(4-methylsulfanylphenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-methylsulfanylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(2-(morpholin-1-yl)ethoxy)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(morpholin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-1-yl)phenyl-

methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(naphth-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl 4-(4-(2-(4-phenoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl) phenylcarbonyl, 4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(2-((phenylmethyl)amino)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(dimethylamino)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-((2-(phenyl)phenylmethyl)-4-methoxypiperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(morpholin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-(2-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(3-(phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-(phenyl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(piperidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl.

[0023] Still another embodiment pertains to compounds having formula (I), or therapeutically acceptable salts, prodrugs or salts of prodrugs thereof, wherein A^1 is $C(A^2)$; A^2 is H, F, CN, C(O)OH, $C(O)OCH_3$ or $C(O)NH_2$; B^1 is (1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((phenylsulfonylmethyl)methyl)propylamino, (1R)-3-oxo-3-(dimethylamino)-1-((pyrimidin-1-ylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-((1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(1,1-dioxothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(N-methyl-N-(1,1-dimethylethyl)amino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(piperidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-amino-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(methylamino)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(morpholin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-oxo-3-(2-(morpholin-1-yl)ethyl)-1-((phenylsulfanyl)methyl)propylamino, (2-phenoxyethyl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)amino, 4-(1-(phenylmethyl)piperidin-4-yl)methylamino, (4-phenyl-1,3-thiazol-2-ylsulfanyl)ethylamino, (1R,2S)-2-(phenylsulfanyl)cyclohex-1-ylamino, (1S,2R)-2-(phenylsulfanyl)cyclohex-1-ylamino, 2-(phenylsulfanyl)cyclopentylamino, 2-(phenylsulfanyl)ethoxy, 2-(phenylsulfanyl)ethylamino, 2-(phenylsulfonyl)ethylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(morpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, 4-(phenylsulfonyl)tetrahydrofuran-3-ylamino, 4-(phenylsulfanyl)tetrahydrofuran-3-ylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propylamino, (1S)-1-((phenylsulfanyl)methyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propylamino), (1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propylamino, (1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-2-ylmethyl)amino)propylamino, (1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethylamino, (3S,4R)-(phenylsulfanyl)pyrrolidin-4-ylamino, 2-(phenylsulfanyl)-1,1-spirobutylethylamino, 2-(phenylsulfanyl)-1,1-spiroethylethylamino, 2-(phenylsulfanyl)-1,1-spiropentylethylamino, piperidin-4-yloxy, (1-propylpiperidin-4-yl)methylamino, pyran-4-ylamino, 2-(pyridin-4-ylsulfanyl)ethylamino, 2-(pyrimidin-2-ylsulfanyl)ethylamino, 1,1-spirobutyl-2-(phenylsulfanyl)ethyl, 2-(thien-2-ylsulfanyl)ethylamino, sulfanylpyran-4-ylamino, (1R)-3-(2-(2H-tetrazol-3-yl)pyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino, (1R)-3-(3-(2H-tetrazol-3-yl)azetidin-1-yl)-1-((phenylsulfanyl)methyl)propylamino or 2-(1,3-thiazol-2-ylsulfanyl)ethylamino; D^1 is H, F, Cl or CF_3; E^1 is H, F or Cl; Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2 or $C(O)NH_2$ and Z^1 is 4-(4-(2-(phenyl)phenylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy))piperidin-1-yl)phenylcarbonyl, 4-(4-((2-(phenyl)pyridin-3-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(piperidin-1-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(pyrid-3-yl)phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-3-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(quinolin-8-ylphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)-4-methoxypiperazin-1-yl)phenylcarbonyl, 4-(4-(2-(thien-2-yl)phenylmethyl)piperazin-1-yl)phenylcarbonyl, 4-(4-(2-(4-trifluoromethoxyphenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl or 4-(4-(2-(4-trifluoromethyl-phenyl)phenylmethyl)piperazin-1-yl)phenylcarbonyl.

[0024] Still another embodiment pertains to compounds having formula (I) which are

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-l-yl)benzoyl)-3-nitrobenzenesulfonamide,

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-

yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-((4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-(4'-phenyl-1,1'-biphenyl-2-ylmethyl)piperazin-1-yl)benzamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl) benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(dimethylamino)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-5-(dimethylamino)-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro-4-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanoic acid,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-4-(phenylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-hydroxy-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(2-naphthyl)benzyl)piperazin-1-yl)ben-

zoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(1-naphthyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((3'-cyano(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((3'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((3'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide
N-(4-(4-((2'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-(2-(1,3-benzodioxol-5-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(3-thienyl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(quinolin-8-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-(2-(1-benzofuran-2-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(quinolin-3-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)cyclopentyl)amino)benzenesulfonamide,
N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethoxy) (1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-y1)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-((phenylsulfa-

nyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfonyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(2-thienyl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((4'-chloro-2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2',4'-difluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(5-methyl-2-thienyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfonyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfonyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1-methyl-4-(phenylsulfanyl)pyrrolidin-3-yl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-bromo(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-(1-(4'-chloro(1,1'-biphenyl)-2-yl)cyclopropyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(dimethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(dimethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2,2-difluoroethyl)amino)-1-((phenyl-

sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-1H-benzimidazole-5-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-1H-1,2,3-benzotriazole-5-sulfonamide,
5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzamide,
N-(4-(4-((4'-(dimethylamino)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-cyano-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)oxy)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)oxy)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
4-(((1R)-3-(bis(2-methoxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(bis(2-methoxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(trifluoromethyl)benzenesulfonamide,
4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-4-yl)methyl)-1-piperazinyl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-methyl-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide,
tert-butyl(5R)-5-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-6-(phenylsulfanyl)hexylcarbamate,
4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-Q-(((1R)-5-((methylsulfonyl)amino)-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-5-((aminocarbonyl)amino)-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-(2-cyclohexylbenzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(morpholin-4-yl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-

1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide, 4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-3-azetidinecarboxylic acid,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)(methyl)amino)acetic acid,
(2R)-1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-2-pyrrolidinecarboxylic acid
1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-4-piperidinecarboxylic acid
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-hydroxyethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(2S)-1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-2-pyrrolidinecarboxylic acid,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(3-(2H-tetrazol-5-yl)azetidin-1-yl)propyl)amino)benzenesulfonamide,
(2S)-2-amino-N-((1S)-2-(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)amino)-1-methyl-2-oxoethyl)propanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(2-(2H-tetrazol-5-yl)pyrrolidin-1-yl)propyl)amino)benzenesulfonamide,

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-(((methylsulfonyl)amino)carbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-N-hydroxy-4-piperidinecarboxamide,
2-chloro-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
2,6-dichloro-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
4-(((1R)-3-((1R,5S)-8-azabicyclo[3.2.1]oct-8-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(7-azabicyclo[2.2.1]hept-7-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(2-(phenylsulfanyl)ethoxy)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(2-(phenylsulfanyl)ethoxy)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
4-(((1R)-3-(7-azabicyclo[2.2.1]hept-7-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexyloxy)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexylmethoxy)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(2-cyclohexylethoxy)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((2-cyclohexylethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexyl(methyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(4,4-dimethylpiperidin-1-yl)-3-nitrobenzenesulfonamide,
tert-butyl 4-(4-(((4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitrophenoxy)-1-piperidinecarboxylate,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(piperidin-4-yloxy)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1-methylpiperidin-4-yl)oxy)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)(propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1-benzylpiperidin-4-yl)methyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)(methyl)amino)-3-nitrobenzenesulfonamide,
4-((1-benzylpiperidin-4-yl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(tetrahydro-2H-sulfanylpyran-4-ylamino)benzenesulfonamide,
ethyl 4-(4-(((4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-1-piperidinecarboxylate,

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1-propylpiperidin-4-yl)methyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(isopropylamino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)ethyl)amino)benzenesulfonamide,
4-((2-(1,3-benzothiazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)benzenesulfonamide,
4-((2-(1,3-benzoxazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-((2-(1,3-benzothiazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(pyrimidin-2-ylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1-benzylpiperidin-4-yl)methyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((2-bromoethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((4-methoxycyclohexyl)methyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(2-thienylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(2-thienylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl) benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(pyrimidin-2-ylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(1,3-thiazol-2-ylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-phenoxyethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-methoxyphenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-methylphenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-chlorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-(((4-fluorophenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-((5-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-2-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-((5-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-2-yl)carbonyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1-cyclohexen-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1-cyclohexen-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-((3aR,6aS)-5-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl-4-(trifluoromethoxy)anilino)carbonyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((2-dimethylanilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((4-methoxy(methyl)anilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((4-dimethylanilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide,
4-(((benzhydryl(methyl)amino)carbonyl)(methyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl((1S)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl(2-(4-methylpiperazin-1-yl)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide,

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl(2-(morpholin-4-yl)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((((1,2-diphenylethyl)(methyl)amino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((((2-(dimethylamino)-1-phenylethyl)(methyl)amino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide,
3-amino-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-(2-(phenylsulfanyl)ethyl)-1H-1,2,3-benzotriazole-5-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-(2-(phenylsulfanyl)ethyl)-1H-benzimidazole-5-sulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-methyl-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopropyl)amino)benzene-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclohexyl)amino)benzene-sulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-methyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1S)-1-methyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R,2S)-2-(phenylsulfanyl)cyclohexyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S,2R)-2-(phenylsulfanyl)cyclohexyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1-(((2-methyl-3-furyl)sulfanyl)methyl)cyclopentyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1-(((2-methyl-3-furyl)sulfanyl)methyl)cyclopentyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-3-pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfanyl)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-' yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfonyl)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(pyridin-4-ylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfonyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(methylsulfonyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(dimethylamino)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(phenylsulfonyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((3S,4R)-(phenylsulfanyl)pyrrolidin-4-yl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propyl)amino)benzenesulfonamide,
N-(4-(4-((3-(4-chlorophenyl)pyridin-4-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((3-(4-chlorophenyl)pyridin-4-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclopenten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-methoxyphenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-fluorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((2-phenyl-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cycloocten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfanyl)phenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide,
(4R)-4-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-5-(phenylsulfanyl)pentanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(dimethylamino)-1-((phenylsulfonyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
2-(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)(methyl)amino)-N,N-dimethylacetamide,
(3R)-N-(tert-butyl)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-diisopropyl-4-(phenylsulfanyl)butanamide,
(3R)-N-(tert-butyl)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-methyl-4-(phenylsulfanyl)butanamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-N-methyl-4-(phenylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-oxo-1-((phenylsulfanyl)methyl)-3-(piperidin-1-yl)propyl)amino)benzenesulfonamide,
N-((5R)-5-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-6-(phenylsulfanyl)hexyl)-2-(dimethylamino)acetamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(phenylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1,1-dioxidothiomorpholin-4-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-cyclopropyl-4-(phenylsulfanyl)butanamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-cyclobutyl-4-(phenylsulfanyl)butanamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-methylpiperazin-1-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

4-(((1R)-3-(azetidin-1-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-(2-(morpholin-4-yl)ethyl)-4-(phenylsulfanyl)butanamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-methyl-4-(phenylsulfanyl)butanamide,
4-(((1R)-3-amino-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-cyano-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(tert-butylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(tert-butyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(piperidin-1-yl)propyl)amino)benzenesulfonamide,
N-(4-,(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(4-acetylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((3R)-3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-((3R)-3-aminopyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(3-hydroxyazetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1,1-dioxidothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(1,3-benzodioxol-5-ylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
4-(((1R)-3-((1,3-benzodioxol-4-ylmethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-2-ylmethyl)amino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
4-(((1R)-3-(bis(2-hydroxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-4-(trifluoromethoxy)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-amino-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-fluorobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-(trifluoromethoxy)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2,5-difluorobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-methylbenzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-4-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3,5-difluorobenzenesulfonamide,
methyl 5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoate,

5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid,
5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid,
5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid,
5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzamide,
5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzamide,
methyl 5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate,
methyl 5-(((4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate,
methyl 5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate,
N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-(2-(1,3-dihydro-2H-isoindol-2-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-(2-(cyclohexylamino)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-(2-(benzylamino)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(piperidin-1-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide,
N-(4-(4-((4-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, and
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-fluoro-3-(trifluoromethyl)benzenesulfonamide, or therapeutically acceptable salts thereof.

[0025] Still another embodiment pertains to compounds having formula (I) or therapeutically acceptable salts thereof as per the appended claim 10.

[0026] In an embodiment, the compound having formula (I) is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide or a therapeutically acceptable salt thereof.

[0027] Still another embodiment pertains to a pharmaceutical composition comprising compounds having formula (I) or their pharmaceutically acceptable salts.

[0028] Still another embodiment pertains to compounds having formula (I) or their pharmaceutically acceptable salts for use in medicine.

[0029] Still another embodiment pertains to compositions for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer,

small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having formula (I).

[0030] Still another embodiment pertains to the use of a compound having formula (I) or therapeutically acceptable salt thereof for manufacturing a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound having formula (I) or therapeutically acceptable salt thereof is adapted for administration to the patient in a therapeutically effective amount.

[0031] In an embodiment of the above use, the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide.

[0032] Still another embodiment pertains to compositions for use in treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said compositions comprising an excipient and a therapeutically effective amount of the compound having formula (I) and a therapeutically effective amount of one additional therapeutic agent or more than one additional therapeutic agent.

[0033] Still another embodiment pertains to the use of a compound having formula (I) or therapeutically acceptable salt thereof and one additional therapeutic agent or more than one additional therapeutic agent for manufacturing a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound having formula (I) or therapeutically acceptable salt thereof and the one additional therapeutic agent or the more than one additional therapeutic agent are adapted for administration to the patient in a therapeutically effective amount.

[0034] In an embodiment of the above use, the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide.

[0035] Still another embodiment pertains to a compound having formula (I) or therapeutically acceptable salt thereof for use in the treatment of bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, wherein the compound having formula (I) or therapeutically acceptable salt thereof is adapted for administration to a patient in a therapeutically effective amount.

[0036] In an embodiment of the above compound for use, the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide.

[0037] Still another embodiment pertains to a compound having formula (I) or therapeutically acceptable salt thereof and one additional therapeutic agent or more than one additional therapeutic agent for use in the treatment of bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, wherein the compound having formula (I) or therapeutically acceptable salt thereof and the one additional therapeutic agent or the more than one additional therapeutic agent are adapted for administration to a patient in a therapeutically effective amount.

[0038] In an embodiment of the above compound for use, the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide.

DETAILED DESCRIPTION OF THE INVENTION

[0039] Variable moieties herein are represented by identifiers (capital letters with numerical and/or alphabetical superscripts) and may be specifically embodied.

[0040] It is meant to be understood that proper valences are maintained for all moieties and combinations thereof, that monovalent moieties having more than one atom are drawn from left to right and are attached through their left ends, and that divalent moieties are also drawn from left to right.

[0041] It is also meant to be understood that a specific embodiment of a variable moiety herein may be the same or different as another specific embodiment having the same identifier.

[0042] The term "cyclic moiety," as used herein, means arene, aryl, cycloalkane, cycloalkyl, cycloalkene, cycloalkenyl, heteroarene, heteroaryl, heterocycloalkane, heterocycloalkyl, heterocycloalkene, heterocycloalkenyl, spiroalkyl, spiroalkenyl, spiroheteroalkyl and spiroheteroalkenyl.

[0043] The term "arene," as used herein, means benzene.

[0044] The term "aryl," as used herein, means phenyl.

[0045] The term "cycloalkane," as used herein, means C_3-cycloalkane, C_4-cycloalkane, C_5-cycloalkane, C_6-cycloalkane, C_7-cycloalkane, C_8-cycloalkane, C_9-cycloalkane, C_{10}-cycloalkane, C_{11}-cycloalkane, C_{12}-cycloalkane, C_{13}-cycloalkane and C_{14}-cycloalkane.

[0046] The term "cycloalkyl," as used herein, means C_3-cycloalkyl, C_4-cycloalkyl, C_5-cycloalkyl C_6-cycloalkyl, C_7-cycloalkyl, C_8-cycloalkyl, C_9-cycloalkyl, C_{10}-cycloalkyl, C_{11}-cycloalkyl, C_{12}-cycloalkyl, C_{13}-cycloalkyl and C_{14}-cycloalkyl.

[0047] The term "cycloalkene," as used herein, means C_4-cycloalkene, C_5-cycloalkene, C_6-cycloalkene, C_7-cycloalkene, C_8-cycloalkene, C_9-cycloalkene, C_{10}-cycloalkene, C_{11}-cycloalkene, C_{12}-cycloalkene, C_{13}-cycloalkene and C_{14}-cycloalkene.

[0048] The term "cycloalkenyl," as used herein, means C_3-cycloalkenyl, C_4-cycloalkenyl, C_5-cycloalkenyl, C_6-cycloalkenyl, C_7-cycloalkenyl, C_8-cycloalkenyl, C_9-cycloalkenyl, C_{10}-cycloalkenyl, C_{11}-cycloalkenyl, C_{12}-cycloalkenyl, C_{13}-cycloalkenyl and C_{14}-cycloalkenyl.

[0049] The term "heteroarene," as used herein, means furan, imidazole, isothiazole, isoxazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, triazine and 1,2,3-triazole.

[0050] The term "heteroaryl," as used herein, means furanyl, imidazolyl, isothiazolyl, isoxazolyl, 1,2,3-oxadiazoyl, 1,2,5-oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrazolyl, thiazolyl, thiophenyl, triazinyl and 1,2,3-triazolyl.

[0051] The term "heterocycloalkane," as used herein, means cycloalkane having one or two or three CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkane having one or two or three CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

[0052] The term "heterocycloalkyl," as used herein, means cycloalkyl having one or two or three CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkyl having one or two or three CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

[0053] The term "heterocycloalkene," as used herein, means cycloalkene having one or two or three CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkene having one or two or three CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

[0054] The term "heterocycloalkenyl," as used herein, means cycloalkenyl having one or two or three CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means cycloalkenyl having one or two or three CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

[0055] The term "spiroalkyl," as used herein, means C_2-spiroalkyl, C_3-spiroalkyl, C_4-spiroalkyl, C_5-spiroalkyl, C_6-spiroalkyl, C_7-spiroalkyl, C_8-spiroalkyl and C_9-spiroalkyl.

[0056] The term "spiroalkenyl," as used herein, means C_2-spiroalkenyl, C_3-spiroalkenyl, C_4-spiroalkenyl, C_5-spiroalkenyl, C_6-spiroalkenyl, C_7-spiroalkenyl, C_8-spiroalkenyl and C_9-spiroalkenyl.

[0057] The term "spiroheteroalkyl," as used herein, means spiroalkyl having one or two CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH.

[0058] The term "spiroheteroalkenyl," as used herein, means spiroalkenyl having one or two CH_2 moieties replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties unreplaced or replaced with N and also means spiroalkenyl having one or two CH_2 moieties unreplaced or replaced with independently selected O, C(O), CNOH, $CNOCH_3$, S, S(O), SO_2 or NH and one or two CH moieties replaced with N.

[0059] The term "alkenyl," as used herein, means C_2-alkenyl, C_3-alkenyl, C_4-alkenyl, C_5-alkenyl and C_6-alkenyl.

[0060] The term "alkyl," as used herein, means C_1-alkyl, C_2-alkyl, C_3-alkyl, C_4-alkyl, C_5-alkyl and C_6-alkyl.

[0061] The term "alkynyl," as used herein, means C_2-alkynyl, C_3-alkynyl, C_4-alkynyl, C_5-alkynyl and C_6-alkynyl.

[0062] The term "C_2-alkenyl," as used herein, means ethenyl (vinyl).

[0063] The term "C_3-alkenyl," as used herein, means 1-propen-1-yl, 1-propen-2-yl (isopropenyl) and 1-propen-3-yl

(allyl).

[0064] The term "C_4-alkenyl," as used herein, means 1-buten-1-yl, 1-buten-2-yl, 1,3-butadien-1-yl, 1,3-butadien-2-yl, 2-buten-1-yl, 2-buten-2-yl, 3-buten-1-yl, 3-buten-2-yl, 2-methyl-1-propen-1-yl and 2-methyl-2-propen-1-yl.

[0065] The term "C_5-alkenyl," as used herein, means 2-methylene-3-buten-1-yl, 2-methylenebut-1-yl, 2-methyl-1-buten-1-yl, 2-methyl-1,3-butadien-1-yl, 2-methyl-2-buten-1-yl, 2-methyl-3-buten-1-yl, 2-methyl-3-buten-2-yl, 3-methyl-1-buten-1-yl, 3-methyl-1-buten-2-yl, 3-methyl-1,3-butadien-1-yl, 3-methyl-1,3-butadien-2-yl, 3-methyl-2-buten-1-yl, 3-methyl-2-buten-2-yl, 3-methyl-3-buten-1-yl, 3-methyl-3-buten-2-yl, 1-penten-1-yl, 1-penten-2-yl, 1-penten-3-yl, 1,3-pentadien-1-yl, 1,3-penta-dien-2-yl, 1,3-pentadien-3-yl, 1,4-pentadien-1-yl, 1,4-pentadien-2-yl, 1,4-pentadien-3-yl, 2-penten-1-yl, 2-penten-2-yl, 2-penten-3-yl, 2,4-pentadien-1-yl, 2,4-pentadien-2-yl, 3-penten-1-yl, 3-penten-2-yl, 4-penten-1-yl and 4-penten-2-yl.

[0066] The term "C_6-alkenyl," as used herein, means 2,2-dimethyl-3-buten-1-yl, 2,3-dimethyl-1-buten-1-yl, 2,3-dimethyl-1,3-butadien-1-yl, 2,3-dimethyl-2-buten-1-yl, 2,3-dimethyl-3-buten-1-yl, 2,3-dimethyl-3-buten-2-yl, 3,3-dimethyl-1-buten-1-yl, 3,3-dimethyl-1-buten-2-yl, 2-ethenyl-1,3-butadien-1-yl, 2-ethenyl-2-buten-1-yl, 2-ethyl-1-buten-1-yl, 2-ethyl-1,3-butadien-1-yl, 2-ethyl-2-buten-1-yl, 2-ethyl-3-buten-1-yl, 1-hexen-1-yl, 1-hexen-2-yl, 1-hexen-3-yl, 1,3-hexadien-1-yl, 1,3-hexadien-2-yl, 1,3-hexadien-3-yl, 1,3,5-hexatrien-1-yl, 1,3,5-hexatrien-2-yl, 1,3,5-hexatrien-3-yl, 1,4-hexadien-1-yl, 1,4-hexadien-2-yl, 1,4-hexadien-3-yl, 1,5-hexadien-1-yl, 1,5-hexadien-2-yl, 1,5-hexadien-3-yl, 2-hexen-1-yl, 2-hexen-2-yl, 2-hexen-3-yl, 2,4-hexadien-1-yl, 2,4-hexadien-2-yl, 2,4-hexadien-3-yl, 2,5-hexadien-1-yl, 2,5-hexadien-2-yl, 2,5-hexadien-3-yl, 3-hexen-1-yl, 3-hexen-2-yl, 3-hexen-3-yl, 3,5-hexadien-1-yl, 3,5-hexadien-2-yl, 3,5-hexadien-3-yl, 4-hexen-1-yl, 4-hexen-2-yl, 4-hexen-3-yl, 5-hexen-1-yl, 5-hexen-2-yl, 5-hexen-3-yl, 2-methylene-3-methyl-3-buten-1-yl, 2-methylene-3-methylbut-1-yl, 2-methylene-3-penten-1-yl, 2-methylene-4-penten-1-yl, 2-methylenepent-1-yl, 2-methylenepent-3-yl, 3-methylene-1-penten-1-yl, 3-methylene-1-penten-2-yl, 3-methylenepent-1-yl, 3-methylene-1,4-pentadien-1-yl, 3-methylene-1,4-pentadien-2-yl, 3-methylene-pent-2-yl, 2-methyl-1-penten-1-yl, 2-methyl-1-penten-3-yl, 2-methyl-1,3-pentadien-1-yl, 2-methyl-1,3-pentadien-3-yl, 2-methyl-1,4-pentadien-1-yl, 2-methyl-1,4-pentadien-3-yl, 2-methyl-2-penten-1-yl, 2-methyl-2-penten-3-yl, 2-methyl-2,4-pentadien-1-yl, 2-methyl-2,4-pentadien-3-yl, 2-methyl-3-penten-1-yl, 2-methyl-3-penten-2-yl, 2-methyl-3-penten-3-yl, 2-methyl-4-penten-1-yl, 2-methyl-4-penten-2-yl, 2-methyl-4-penten-3-yl, 3-methyl-1-penten-1-yl, 3-methyl-1-penten-2-yl, 3-methyl-1,3-pentadien-1-yl, 3-methyl-1,3-pentadien-2-yl, 3-methyl-1,4-pentadien-1-yl, 3-methyl-1,4-pentadien-2-yl, 3-methyl-2-penten-1-yl, 3-methyl-2-penten-2-yl, 3-methyl-2,4-pentadien-1-yl, 3-methyl-3-penten-1-yl, 3-methyl-3-penten-2-yl, 3-methyl-4-penten-1-yl, 3-methyl-4-penten-2-yl, 3-methyl-4-penten-3-yl, 4-methyl-1-penten-1-yl, 4-methyl-1-penten-2-yl, 4-methyl-1-penten-3-yl, 4-methyl-1,3-pentadien-1-yl, 4-methyl-1,3-pentadien-2-yl, 4-methyl-1,3-pentadien-3-yl, 4-methyl-1,4-pentadien-1-yl, 4-methyl-1,4-pentadien-2-yl, 4-methyl-1,4-pentadien-3-yl, 4-methylene-2-penten-3-yl, 4-methyl-2-penten-1-yl, 4-methyl-2-penten-2-yl, 4-methyl-2-penten-3-yl, 4-methyl-2,4-pentadien-1-yl, 4-methyl-2,4-pentadien-2-yl, 4-methyl-3-penten-1-yl, 4-methyl-3-penten-2-yl, 4-methyl-3-penten-3-yl, 4-methyl-4-penten-1-yl and 4-methyl-4-penten-2-yl.

[0067] The term "C_1-alkyl," as used herein, means methyl.

[0068] The term "C_2-alkyl," as used herein, means ethyl.

[0069] The term "C_3-alkyl," as used herein, means prop-1-yl and prop-2-yl (isopropyl).

[0070] The term "C_4-alkyl," as used herein, means but-1-yl, but-2-yl, 2-methylprop-1-yl and 2-methylprop-2-yl (tert-butyl).

[0071] The term "C_5-alkyl," as used herein, means 2,2-dimethylprop-1-yl (neo-pentyl), 2-methylbut-1-yl, 2-methylbut-2-yl, 3-methylbut-1-yl, 3-methylbut-2-yl, pent-1-yl, pent-2-yl and pent-3-yl.

[0072] The term "C_6-alkyl," as used herein, means 2,2-dimethylbut-1-yl, 2,3-dimethylbut-1-yl, 2,3-dimethylbut-2-yl, 3,3-dimethylbut-1-yl, 3,3-dimethylbut-2-yl, 2-ethylbut-1-yl, hex-1-yl, hex-2-yl, hex-3-yl, 2-methylpent-1-yl, 2-methylpent-2-yl, 2-methylpent-3-yl, 3-methylpent-1-yl, 3-methylpent-2-yl, 3-methylpent-3-yl, 4-methylpent-1-yl and 4-methylpent-2-yl.

[0073] The term "C_2-alkynyl," as used herein, means ethynyl (acetylenyl).

[0074] The term "C_3-alkynyl," as used herein, means 1-propyn-1-yl and 2-propyn-1-yl (propargyl).

[0075] The term "C_4-alkynyl," as used herein, means 1-butyn-1-yl, 1,3-butadiyn-1-yl, 2-butyn-1-yl, 3-butyn-1-yl and 3-butyn-2-yl.

[0076] The term "C_5-alkynyl," as used herein, means 2-methyl-3-butyn-1-yl, 2-methyl-3-butyn-2-yl, 3-methyl-1-butyn-1-yl, 1,3-pentadiyn-1-yl, 1,4-pentadiyn-1-yl, 1,4-pentadiyn-3-yl, 2,4-pentadiyn-1-yl, 1-pentyn-1-yl, 1-pentyn-3-yl, 2-pentyn-1-yl, 3-pentyn-1-yl, 3-pentyn-2-yl, 4-pentyn-1-yl and 4-pentyn-2-yl.

[0077] The term "C_6-alkynyl," as used herein, means 2,2-dimethyl-3-butyn-1-yl, 3,3-dimethyl-1-butyn-1-yl, 2-ethyl-3-butyn-1-yl, 2-ethynyl-3-butyn-1-yl, 1-hexyn-1-yl, 1-hexyn-3-yl, 1,3-hexadiyn-1-yl, 1,3,5-hexatriyn-1-yl, 1,4-hexadiyn-1-yl, 1,4-hexadiyn-3-yl, 1,5-hexadiyn-1-yl, 1,5-hexadiyn-3-yl, 2-hexyn-1-yl, 2,5-hexadiyn-1-yl, 3-hexyn-1-yl, 3-hexyn-2-yl, 3,5-hexadiyn-2-yl, 4-hexyn-1-yl, 4-hexyn-2-yl, 4-hexyn-3-yl, 5-hexyn-1-yl, 5-hexyn-2-yl, 5-hexyn-3-yl, 2-methyl-3-pentyn-1-yl, 2-methyl-3-pentyn-2-yl, 2-methyl-4-pentyn-1-yl, 2-methyl-4-pentyn-2-yl, 2-methyl-4-pentyn-3-yl, 3-methyl-1-pentyn-1-yl, 3-methyl-4-pentyn-1-yl, 3-methyl-4-pentyn-2-yl, 3-methyl-1,4-pentadiyn-1-yl, 3-methyl-1,4-pentadiyn-3-yl, 3-methyl-4-pentyn-1-yl, 3-methyl-4-pentyn-3-yl, 4-methyl-1-pentyn-1-yl and 4-methyl-2-pentyn-1-yl.

[0078] The term "C_4-cycloalkane," as used herein, means cyclobutane.

[0079] The term "C_5-cycloalkane," as used herein, means cyclopentane.

[0080] The term "C_6-cycloalkane," as used herein, means cyclohexane.

[0081] The term "C_7-cycloalkane, " as used herein, means cycloheptane.

[0082] The term "C_8-cycloalkane," as used herein, means cyclooctane.

[0083] The term "C_9-cycloalkane," as used herein, means cyclononane.

[0084] The term "C_{10}-cycloalkane," as used herein, means cyclodecane.

[0085] The term "C_{11}-cycloalkane," as used herein, means cycloundecane.

[0086] The term "C_{12}-cycloalkane," as used herein, means cyclododecane.

[0087] The term "C_{13}-cycloalkane," as used herein, means cyclotridecane.

[0088] The term "C_{14}-cycloalkane," as used herein, means cyclotetradecane.

[0089] The term "C_4-cycloalkene," as used herein, means cyclobutene and 1,3-cyclobutadiene.

[0090] The term "C_5-cycloalkene," as used herein, means cyclopentene and 1,3-cyclopentadiene.

[0091] The term "C_6-cycloalkene," as used herein, means cyclohexene, 1,3-cyclohexadiene and 1,4-cyclohexadiene.

[0092] The term "C_7-cycloalkene," as used herein, means cycloheptene and 1,3-cycloheptadiene.

[0093] The term "C_8-cycloalkene," as used herein, means cyclooctene, 1,3-cyclooctadiene, 1,4-cyclooctadiene, 1,5-cyclooctadiene, 1,3,5-cyclooctatriene and 1,3,6-cyclooctatriene.

[0094] The term "C_9-cycloalkene," as used herein, means cyclononene, 1,3-cyclononadiene, 1,4-cyclononadiene, 1,5-cyclononadiene, 1,3,5-cyclononatriene, 1,3,6-cyclononatriene, 1,3,7-cyclononatriene and 1,3,5,7-cyclononatetraene.

[0095] The term "C_{10}-cycloalkene," as used herein, means cyclodecene, 1,3-cyclodecadiene, 1,4-cyclodecadiene, 1,5-cyclodecadiene, 1,6-cyclodecadiene, 1,3,5-cyclodecatriene, 1,3,6-cyclodecatriene, 1,3,5,7-cyclodecatetraene, 1,3,5,8-cyclodecatetraene and 1,3,6,8-cyclodecatetraene.

[0096] The term "C_{11}-cycloalkene," as used herein, means cycloundecene, 1,3-cycloundecadiene, 1,4-cycloundecadiene, 1,5-cycloundecadiene, 1,6-cycloundecadiene, 1,3,5-cycloundecatriene, 1,3,6-cycloundecatriene, 1,3,7-cycloundecatriene, 1,4,7-cycloundecatriene, 1,4,8-cycloundecatriene; 1,3,5,7-cycloundecatetraene, 1,3,5,8-cycloundecatetraene, 1,3,6,8-cycloundecatetraene and 1,3,5,7,9-cycloundecapentaene.

[0097] The term "C_{12}-cycloalkene," as used herein, means cyclododecene, 1,3-cyclododecadiene, 1,4-cyclododecadiene, 1,5-cyclododecadiene, 1,6-cyclododecadiene, 1,7-cyclododecadiene, 1,3,5-cyclododecatriene, 1,3,6-cyclododecatriene, 1,3,7-cyclododecatriene, 1,3,8-cyclododecatriene, 1,4,7-cyclododecatriene, 1,4,8-cyclododecatriene, 1,5,9-cyclododecatriene, 1,3,5,7-cyclododecatetraene, 1,3,5,8-cyclododecatetraene, 1,3,5,9-cyclododecatetraene, 1,3,6,8-cyclododecatetraene, 1,3,6,9-cyclododecatetraene, 1,3,6,10-cyclododecatetraene, 1,3,7,9-cyclododecatetraene, 1,4,7,10-cyclododecatetraene, 1,3,5,7,9-cyclododecapentaene, 1,3,5,7,10-cyclododecapentaene and 1,3,5,8,10-cyclododecapentaene.

[0098] The term "C_{13}-cycloalkene," as used herein, means 1,3-cyclotridecadiene, 1,4-cyclotridecadiene, 1,5-cyclotridecadiene, 1,6-cyclotridecadiene, 1,7-cyclotridecadiene, 1,3,5-cyclotridecatriene, 1,3,6-cyclotridecatriene, 1,3,7-cyclotridecatriene, 1,3,8-cyclotridecatriene, 1,4,7-cyclotridecatriene, 1,4,8-cyclotridecatriene, 1,4,9-cyclotridecatriene, 1,5,9-cyclotridecatriene, 1,3,5,7-cyclotridecatetraene, 1,3,5,8-cyclotridecatetraene, 1,3,5,9-cyclotridecatetraene, 1,3,6,8-cyclotridecatetraene, 1,3,6,9-cyclotridecatetraene, 1,3,6,10-cyclotridecatetraene, 1,3,6,11-cyclotridecatetraene, 1,3,7,9-cyclotridecatetraene, 1,3,7,10-cyclotridecatetraene, 1,4,7,10-cyclotridecatetraene, 1,3,6,11-cyclotridecatetraene, 1,3,,5,7,9-cyclotridecapentaene, 1,3,5,7,10-cyclotridecapentaene, 1,3,5,8,10-cyclotridecapentaene, 1,3,5,8,11-cyclotridecapentaene, 1,3,6,8,11-cyclotridecapentaene and 1,3,5,7,9,11-cyclotridecahexaene.

[0099] The term "C_{14}-cycloalkene," as used herein, means cyclotetradecene, 1,3-cyclotetradecadiene, 1,4-cyclotetradecadiene, 1,5-cyclotetradecadiene, 1,6-cyclotetradecadiene, 1,7-cyclotetradecadiene, 1,8-cyclotetradecadiene, 1,3,5-cyclotetradecatriene, 1,3,6-cyclotetradecatriene, 1,3,7-cyclotetradecatriene, 1,3,8-cyclotetradecatriene, 1,3,9-cyclotetradecatriene, 1,4,7-cyclotetradecatriene, 1,4,8-cyclotetradecatriene, 1,4,9-cyclotetradecatriene, 1,5,9-cyclotetradecatriene, 1,5,10-cyclotetradecatriene, 1,3,5,7-cyclotetradecatetraene, 1,3,5,8-cyclotetradecatetraene, 1,3,5,9-cyclotetradecatetraene, 1,3,5,10-cyclotetradecatetraene, 1,3,6,8-cyclotetradecatetraene, 1,3,6,9-cyclotetradecatetraene, 1,3,6,10-cyclotetradecatetraene, 1,3,6,11-cyclotetradecatetraene, 1,3,6,12-cyclotetradecatetraene, 1,3,7,9-cyclotetradecatetraene, 1,3,7,10-cyclotetradecatetraene, 1,3,7,11-cyclotetradecatetraene, 1,3,8,10-cyclotetradecatetraene, 1,4,7,10-cyclotetradecatetraene, 1,4,7,11-cyclotetradecatetraene, 1,4,8,11-cyclotetradecatetraene, 1,3,5,7,9-cyclotetradecapentaene, 1,3,5,7,10-cyclotetradecapentaene, 1,3,5,7,11-cyclotetradecapentaene, 1,3,5,8,10-cyclotetradecapentaene, 1,3,5,8,11-cyclotetradecapentaene, 1,3,5,8,12-cyclotetradecapentaene, 1,3,5,9,11-cyclotetradecapentaene, 1,3,5,8,11-cyclotetradecapentaene, 1,3,6,8,11-cyclotetradecapentaene, 1,3,6,9,11-cyclotetradecapentaene, 1,3,6,9,12-cyclotetradecapentaene, 1,3,5,8,11-cyclotetradecapentaene, 1,3,5,8,12-cyclotetradecapentaene, 1,3,5,7,9,11-cyclotetradecahexaene, 1,3,5,7,9,12-cyclotetradecahexaene, 1,3,5,7,10,12-cyclotetradecahexaene, 1,3,5,8,10,12-cyclotetradecahexaene and 1,3,5,7,9,11,13-cyclotetradecaheptaene.

[0100] The term "C_3-cycloalkenyl," as used herein, means cycloprop-1-en-1-yl and cycloprop-2-en-1-yl.

[0101] The term "C_4-cycloalkenyl," as used herein, means cyclobut-1-en-1-yl and cyclobut-2-en-1-yl.

[0102] The term "C_5-cycloalkenyl," as used herein, means cyclopent-1-en-1-yl, cyclopent-2-en-1-yl, cyclopent-3-en-1-yl and cyclopenta-1,3-dien-1-yl.

[0103] The term "C_6-cycloalkenyl," as used herein, means cyclohex-1-en-1-yl, cyclohex-2-en-1-yl, cyclohex-3-en-1-yl, cyclohexa-1,3-dien-1-yl, cyclohexa-1,4-dien-1-yl, cyclohexa1,5-dien-1-yl, cyclohexa-2,4-dien-1-yl and cyclohexa-2,5-dien-1-yl.

[0104] The term "C_7-cycloalkenyl," as used herein, means bicyclo[2.2.1]hept-2-en-1-yl, bicyclo[2.2.1]hept-2-en-2-yl, bicyclo[2.2.1]hept-2-en-5-yl, bicyclo[2.2.1]hept-2-en-7-yl, bicyclo[2.2.1]hepta-2,5-dien-1-yl, bicyclo[2.2.1]hepta-2,5-dien-2-yl, bicyclo[2.2.1]hepta-2,5-dien-7-yl, cyclohept-1-en-1-yl, cyclohept-2-en-1-yl, cyclohept-3-en-1-yl, cyclohept-4-en-1-yl, cyclohepta-1,3-dien-1-yl, cyclohepta-1,4-dien-1-yl, cyclohepta-1,5-dien-1-yl, cyclohepta-1,6-dien-1-yl, cyclohepta-2,4-dien-1-yl, cyclohepta-2,5-dien-1-yl, cyclohepta-2,6-dien-1-yl, cyclohepta-3,5-dien-1-yl, cyclohepta-1,3,5-trien-1-yl, cyclohepta-1,3,6-trien-1-yl, cyclohepta-1,4,6-trien-1-yl and cyclohepta-2,4,6-trien-1-yl.

[0105] The term "C_8-cycloalkenyl," as used herein, means bicyclo[2.2.2]oct-2-en-1-yl, bicyclo[2.2.2]oct-2-en-2-yl, bicyclo[2.2.2]oct-2-en-5-yl, bicyclo[2.2.2]oct-2-en-7-yl, bicyclo[2.2.2]octa-2,5-dien-1-yl, bicyclo[2.2.2]octa-2,5-dien-2-yl, bicyclo[2.2.2]octa-2,5-dien-7-yl, bicyclo[2.2.2]octa-2,5,7-trien-1-yl, bicyclo[2.2.2]octa-2,5,7-trien-2-yl cyclooct-1-en-1-yl, cyclooct-2-en-1-yl, cyclooct-3-en-1-yl, cyclooct-4-en-1-yl, cycloocta-1,3-dien-1-yl, cycloocta-1,4-dien-1-yl, cycloocta-1,5-dien-1-yl, cycloocta-1,6-dien-1-yl, cyclooctal,7-dien-1-yl, cycloocta-2,4-dien-1-yl, cycloocta-2,5-dien-1-yl, cycloocta-2,6-dien-1-yl, cycloocta-2,7-dien-1-yl, cycloocta-3,5-dien-1-yl, cycloocta-3,6-dien-1-yl, cycloocta-1,3,5-trien-1-yl, cycloocta-1,3,6-trien-1-yl, cycloocta-1,3,7-trien-1-yl, cycloocta-1,4,6-trien-1-yl, cycloocta-1,4,7-trien-1-yl, cycloocta-1,5,7-trien-1-yl, cycloocta-2,4,6-trien-1-yl, cycloocta-2,4,7-trien-1-yl, cycloocta-2,5,7-trien-1-yl and cycloocta-1,3,5,7-tetraen-1-yl.

[0106] The term "C_9-cycloalkenyl," as used herein, means cyclonon-1-en-1-yl, cyclonon-2-en-1-yl, cyclonon-3-en-1-yl, cyclonon-4-en-1-yl, cyclonon-5-en-1-yl, cyclonona-1,3-dien-1-yl, cyclonona-1,4-dien-1-yl, cyclonona-1,5-dien-1-yl, cyclonona-1,6-dien-1-yl, cyclonona-1,7-dien-1-yl, cyclonona-1,8-dien-1-yl, cyclonona-2,4-dien-1-yl, cyclonona-2,5-dien-1-yl, cyclonona-2,6-dien-1-yl, cyclonona-2,7-dien-1-yl, cyclonona-2,8-dien-1-yl, cyclonona-3,5-dien-1-yl, cyclonona-3,6-dien-1-yl, cyclonona-3,7-dien-1-yl, cyclonona-4,6-dien-1-yl, cyclonona-1,3,5-trien-1-yl, cyclonona-1,3,6-trien-1-yl, cyclonona-1,3,7-trien-1-yl, cyclonona-1,3,8-trien-1-yl, cyclonona-1,4,6-trien-1-yl, cyclonona-1,4,7-trien-1-yl, cyclonona-1,4,8-trien-1-yl, cyclonona-1,5,7-trien-1-yl, cyclonona-1,5,8-trien-1-yl, cyclonona-1,6,8-trien-1-yl, cyclonona-2,4,8-trien-1-yl, cyclonona-2,4,6-trien-1-yl, cyclonona-2,4,7-trien-1-yl, cyclonona-2,4,8-trien-1-yl, cyclonona-2,5,7-trien-1-yl, cyclonona-2,5,8-trien-1-yl, cyclonona-1,3,5,7-tetraen-1-yl, cyclonona-1,3,5,8-tetraen-1-yl, cyclonona-1,3,6,8-tetraen-1-yl, cyclonona-1,4,6,8-tetraen-1-yl and cyclonona-2,4,6,8-tetraen-1-yl.

[0107] The term "C_{10}-cycloalkenyl," as used herein, means cyclodec-1-en-1-yl, cyclodec-2-en-1-yl, cyclodec-3-en-1-yl, cyclodec-4-en-1-yl, cyclodec-5-en-1-yl, cyclodeca-1,3-dien-1-yl, cyclodeca-1,4-dien-1-yl, cyclodeca-1,5-dien-1-yl, cyclodeca-1,6-dien-1-yl, cyclodeca-1,7-dien-1-yl, cyclodeca-1,8-dien-1-yl, cyclodeca-1,9-dien-1-yl, cyclodeca-2,4-dien-1-yl, cyclodeca-2,5-dien-1-yl, cyclodeca-2,6-dien-1-yl, cyclodeca-2,7-dien-1-yl, cyclodeca-2,8-dien-1-yl, cyclodeca-2,9-dien-1-yl, cyclodeca-3,5-dien-1-yl, cyclodeca-3,6-dien-1-yl, cyclodeca-3,7-dien-1-yl, cyclodeca-3,8-dien-1-yl, cyclodeca-4,6-dien-1-yl, cyclodeca-4,7-dien-1-yl, cyclodeca-1,3,5-trien-1-yl, cyclodeca-1,3,6-trien-1-yl, cyclodeca-1,3,7-trien-1-yl, cyclodeca-1,3,8-trien-1-yl, cyclodeca-1,3,9-trien-1-yl, cyclodeca-1,4,6-trien-1-yl, cyclodeca-1,4,7-trien-1-yl, cyclodeca-1,4,8-trien-1-yl, cyclodeca-1,4,9-trien-1-yl, cyclodeca-1,5,7-trien-1-yl, cyclodeca-1,5,8-trien-1-yl, cyclodeca-1,5,9-trien-1-yl, cyclodeca-1,6,8-trien-1-yl, cyclodeca-1,6,9-trien-1-yl, cyclodeca-1,7,9-trien-1-yl, cyclodeca-2,4,6-trien-1-yl, cyclodeca-2,4,7-trien-1-yl, cyclodeca-2,4,8-trien-1-yl, cyclodeca-2,4,9-trien-1-yl, cyclodeca-2,5,7-trien-1-yl, cyclodeca-2,5,8-trien-1-yl, cyclodeca-2,5,9-trien-1-yl, cyclodeca-2,6,8-trien-1-yl, cyclodeca-3,5,7-trien-1-yl, cyclodeca-3,5,8-trien-1-yl, cyclodeca-1,3,5,7-tetraen-1-yl, cyclodeca-1,3,5,8-tetraen-1-yl, cyclodeca-1,3,5,9-tetraen-1-yl, cyclodeca-1,3,6,8-tetraen-1-yl, cyclodeca-1,3,6,9-tetraen-1-yl, cyclodeca-1,3,7,9-tetraen-1-yl, cyclodeca-1,4,6,8-tetraen-1-yl, cyclodeca-1,4,6,9-tetraen-1-yl, cyclodeca-1,4,7,9-tetraen-1-yl, cyclodeca-1,5,7,9-tetraen-1-yl, cyclodeca-2,4,6,8-tetraen-1-yl, cyclodeca-2,4,6,9-tetraen-1-yl, cyclodeca-2,4,7,9-tetraen-1-yl and cyclodeca-1,3,5,7,9-pentaen-1-yl.

[0108] The term "C_{11}-cycloalkenyl," as used herein, means cycloundec-1-en-1-yl, cycloundec-2-en-1-yl, cycloundec-3-en-1-yl, cycloundec-4-en-1-yl, cycloundec-5-en-1-yl, cycloundec-6-en-1-yl, cycloundeca-1,3-dien-1-yl, cycloundeca-1,4-dien-1-yl, cycloundeca-1,5-dien-1-yl, cycloundeca-1,6-dien-1-yl, cycloundeca-1,7-dien-1-yl, cycloundeca-1,8-dien-1-yl, cycloundeca-1,9-dien-1-yl, cycloundeca-1,10-dien-1-yl, cycloundeca-2,4-dien-1-yl, cycloundeca-2,5-dien-1-yl, cycloundeca-2,6-dien-1-yl, cycloundeca-2,7-dien-1-yl, cycloundeca-2,8-dien-1-yl, cycloundeca-2,9-dien-1-yl, cycloundeca-2,10-dien-1-yl, cycloundeca-3,5-dien-1-yl, cycloundeca-3,6-dien-1-yl, cycloundeca-3,7-dien-1-yl, cycloundeca-3,8-dien-1-yl, cycloundeca-3,9-dien-1-yl, cycloundeca-4,6-dien-1-yl, cycloundeca-4,7-dien-1-yl, cycloundeca-4,8-dien-1-yl, cycloundeca-5,7-dien-1-yl, cycloundeca-1,3,5-trien-1-yl, cycloundeca-1,3,6-trien-1-yl, cycloundeca-1,3,7-trien-1-yl, cycloundeca-1,3,8-trien-1-yl, cycloundeca-1,3,9-trien-1-yl, cycloundeca-1,3,10-trien-1-yl, cycloundeca-1,4,6-trien-1-yl, cycloundeca-1,4,7-tri-en-1-yl, cycloundeca-1,4,8-trien-1-yl, cycloundeca-1,4,9-trien-1-yl, cycloundeca-1,4,10-trien-1-yl, cycloundeca-1,5,7-trien-1-yl, cycloundeca-1,5,8-trien-1-yl, cycloundeca-1,5,9-trien-1-yl, cycloundeca-1,5,10-trien-1-yl, cycloundeca-1,6,8-trien-1-yl, cycloundeca-1,6,9-trien-1-yl, cycloundeca-1,6,10-trien-1-yl, cycloundeca-1,7,9-trien-1-yl, cycloundeca-1,7,10-trien-1-yl, cycloundeca-1,8,10-trien-1-yl, cycloundeca-2,4,6-trien-1-yl, cycloundeca-2,4,7-trien-1-yl,

cycloundeca-2,4,8-trien-1-yl, cycloundeca-2,4,9-trien-1-yl, cycloundeca-2,4,10-trien-1-yl, cycloundeca-2,5,7-trien-1-yl, cycloundeca-2,5,8-trien-1-yl, cycloundeca-2,5,9-trien-1-yl, cycloundeca-2,5,10-tri-en-1-yl, cycloundeca-2,6,8-trien-1-yl, cycloundeca-2,6,9-trien-1-yl, cycloundeca-2,6,10-trien-1-yl, cycloundeca-2,7,9-trien-1-yl, cycloundeca-3,5,7-trien-1-yl, cycloundeca-3,5,8-trien-1-yl, cycloundeca-3,5,9-trien-1-yl, cycloundeca-3,6,8-trien-1-yl, cycloundeca-3,6,9-trien-1-yl, cycloundeca-4,6,8-trien-1-yl, cycloundeca-1,3,5,7-tetraen-1-yl, cycloundeca-1,3,5,8-tetraen-1-yl, cycloundeca-1,3,5,9-tetraen-1-yl, cycloundeca-1,3,5,10-tetraen-1-yl, cycloundeca-1,3,6,8-tetraen-1-yl, cycloundeca-1,3,6,9-tetraen-1-yl, cycloundeca-1,3,6,10-tetraen-1-yl, cycloundeca-1,3,7,9-tetraen-1-yl, cycloundeca-1,3,7,10-tetraen-1-yl, cycloundeca-1,3,8,10-tetraen-1-yl, cycloundeca-1,4,6,8-tetraen-1-yl, cycloundeca-1,4,6,9-tetraen-1-yl, cycloundeca-1,4,6,10-tetraen-1-yl, cycloundeca-1,4,8,10-tetraen-1-yl, cycloundeca-1,5,7,9-tetraen-1-yl, cycloundeca-1,5,7,10-tetraen-1-yl, cycloundeca-1,5,8,10-tetraen-1-yl, cycloundeca-1,6,8,10-tetraen-1-yl, cycloundeca-2,4,6,8-tetraen-1-yl, cycloundeca-2,4,6,9-tetraen-1-yl, cycloundeca-2,4,6,10-tetraen-1-yl, cycloundeca-2,4,7,9-tetraen-1-yl, cycloundeca-2,5,7,9-tetraen-1-yl, cycloundeca-3,5,7,9-tetraen-1-yl, cycloundeca-1,3,5,7,9-pentaenyl, cycloundeca-1,3,5,7,10-pentaenyl, cycloundeca-1,3,5,8,10-pentaenyl, cycloundeca-1,3,6,8,10-pentaenyl, cycloundeca-1,4,6,8,10-pentaenyl and cycloundeca-2,4,6,8,10-pentaenyl.

[0109] The term "C_{12}-cycloalkenyl," as used herein, means cyclododec-1-en-1-yl, cyclododec-2-en-1-yl, cyclododec-3-en-1-yl, cyclododec-4-en-1-yl, cyclododec-5-en-1-yl, cyclododec-6-en-1-yl, cyclododeca-1,3-dien-1-yl, cyclododeca-1,4-dien-1-yl, cyclododeca-1,5-dien-1-yl, cyclododeca-1,6-dien-1-yl, cyclododeca-1,7-dien-1-yl, cyclododeca-1,8-dien-1-yl, cyclododeca-1,9-dien-1-yl, cyclododeca-1,10-dien-1-yl, cyclododeca-1,11-dien-1-yl, cyclododeca-2,4-dien-1-yl, cyclododeca-2,5-dien-1-yl, cyclododeca-2,6-dien-1-yl, cyclododeca-2,7-dien-1-yl, cyclododeca-2,8-dien-1-yl, cyclododeca-2,9-dien-1-yl, cyclododeca-2,10-dien-1-yl, cyclododeca-2,11-dien-1-yl, cyclododeca-3,5-dien-1-yl, cyclododeca-3,6-dien-1-yl, cyclododeca-3,7-dien-1-yl, cyclododeca-3,8-dien-1-yl, cyclododeca-3,9-dien-1-yl, cyclododeca-3,10-dien-1-yl, cyclododeca-3,11-dien-1-yl, cyclododeca-4,6-dien-1-yl, cyclododeca-4,7-dien-1-yl, cyclododeca-4,8-dien-1-yl, cyclododeca-4,9-dien-1-yl, cyclododeca-5,7-dien-1-yl, cyclododeca-5,8-dien-1-yl, cyclododeca-1,3,5-trien-1-yl, cyclododeca-1,3,6-trien-1-yl, cyclododeca-1,3,7-trien-1-yl, cyclododeca-1,3,8-trien-1-yl, cyclododeca-1,3,9-trien-1-yl, cyclododeca-1,3,10-trien-1-yl, cyclododeca-1,3,11-trien-1-yl, cyclododeca-1,4,6-trien-1-yl, cyclododeca-1,4,7-trien-1-yl, cyclododeca-1,4,8-trien-1-yl, cyclododeca-1,4,9-trien-1-yl, cyclododeca-1,4,10-trien-1-yl, cyclododeca-1,4,11-trien-1-yl, cyclododeca-1,5,7-trien-1-yl, cyclododeca-1,5,8-trien-1-yl, cyclododeca-1,5,9-trien-1-yl, cyclododeca-1,5,10-trien-1-yl, cyclododeca-1,5,11-trien-1-yl, cyclododeca-1,6,8-trien-1-yl, cyclododeca-1,6,9-trien-1-yl, cyclododeca-1,6,10-trien-1-yl, cyclododeca-1,6,11-trien-1-yl, cyclododeca-1,7,9-trien-1-yl, cyclododeca-1,7,10-trien-1-yl, cyclododeca-1,7,11-trien-1-yl, cyclododeca-1,8,10-trien-1-yl, cyclododeca-1,8,11-trien-1-yl, cyclododeca-1,9,11-trien-1-yl, cyclododeca-2,4,6-trien-1-yl, cyclododeca-2,4,7-trien-1-yl, cyclododeca-2,4,8-trien-1-yl, cyclododeca-2,4,9-trien-1-yl, cyclododeca-2,4,10-trien-1-yl, cyclododeca-2,4,11-trien-1-yl, cyclododeca-2,5,7-trien-1-yl, cyclododeca-2,5,8-trien-1-yl, cyclododeca-2,5,9-trien-1-yl, cyclododeca-2,5,10-trien-1-yl, cyclododeca-2,5,11-trien-1-yl, cyclododeca-2,6,8-trien-1-yl, cyclododeca-2,6,9-trien-1-yl, cyclododeca-2,6,10-trien-1-yl, cyclododeca-2,6,11-trien-1-yl, cyclododeca-2,7,9-trien-1-yl, cyclododeca-2,7,10-trien-1-yl, cyclododeca-2,8,10-trien-1-yl, cyclododeca-3,5,7-trien-1-yl, cyclododeca-3,5,8-trien-1-yl, cyclododeca-3,5,9-trien-1-yl, cyclododeca-3,5,10-trien-1-yl, cyclododeca-3,6,8-trien-1-yl, cyclododeca-3,6,9-trien-1-yl, cyclododeca-3,6,10-trien-1-yl, cyclododeca-3,7,9-trien-1-yl, cyclododeca-4,6,8-trien-1-yl, cyclododeca-4,6,9-trien-1-yl, cyclododeca-1,3,5,7-tetraen-1-yl, cyclododeca-1,3,5,8-tetraen-1-yl, cyclododeca-1,3,5,9-tetraen-1-yl, cyclododeca-1,3,5,10-tetraen-1-yl, cyclododeca-1,3,5,11-tetraen-1-yl, cyclododeca-1,3,6,8-tetraen-1-yl, cyclododeca-1,3,6,9-tetraen-1-yl, cyclododeca-1,3,6,10-tetraen-1-yl, cyclododeca-1,3,6,11-tetraen-1-yl, cyclododeca-1,3,7,9-tetraen-1-yl, cyclododeca-1,3,7,10-tetraen-1-yl, cyclododeca-1,3,7,11-tetraen-1-yl, cyclododeca-1,3,8,10-tetraen-1-yl, cyclododeca-1,3,8,11-tetraen-1-yl, cyclododeca-1,3,9,11-tetraen-1-yl, cyclododeca-1,4,6,8-tetraen-1-yl, cyclododeca-1,4,6,9-tetraen-1-yl, cyclododeca-1,4,6,10-tetraen-1-yl, cyclododeca-1,4,6,11-tetraen-1-yl, cyclododeca-1,4,7,9-tetraen-1-yl, cyclododeca-1,4,7,10-tetraen-1-yl, cyclododeca-1,4,7,11-tetraen-1-yl, cyclododeca-1,4,8,10-tetraen-1-yl, cyclododeca-1,4,8,11-tetraen-1-yl, cyclododeca-1,4,9,11-tetraen-1-yl, cyclododeca-1,5,7,9-tetraen-1-yl, cyclododeca-1,5,7,10-tetraen-1-yl, cyclododeca-1,5,7,11-tetraen-1-yl, cyclododeca-1,5,8,10-tetraen-1-yl, cyclododeca-1,5,8,11-tetraen-1-yl, cyclododeca-1,5,9,11-tetraen-1-yl, cyclododeca-1,6,8,10-tetraen-1-yl, cyclododeca-1,6,8,11-tetraen-1-yl, cyclododeca-1,6,9,11-tetraen-1-yl, cyclododeca-1,7,9,11-tetraen-1-yl, cyclododeca-2,4,6,8-tetraen-1-yl, cyclododeca-2,4,6,9-tetraen-1-yl, cyclododeca-2,4,6,10-tetraen-1-yl, cyclododeca-2,4,6,11-tetraen-1-yl, cyclododeca-2,4,7,9-tetraen-1-yl, cyclododeca-2,4,7,10-tetraen-1-yl, cyclododeca-2,4,7,11-tetraen-1-yl, cyclododeca-2,4,8,10-tetraen-1-yl, cyclododeca-2,4,8,11-tetraen-1-yl, cyclododeca-2,4,9,11-tetraen-1-yl, cyclododeca-2,5,7,9-tetraen-1-yl, cyclododeca-2,5,7,10-tetraen-1-yl, cyclododeca-2,5,7,11-tetraen-1-yl, cyclododeca-2,5,8,10-tetraen-1-yl, cyclododeca-2,5,8,11-tetraen-1-yl, cyclododeca-2,6,8,10-tetraen-1-yl, cyclododeca-3,5,7,9-tetraen-1-yl, cyclododeca-3,5,7,10-tetraen-1-yl, cyclododeca-3,5,8,10-tetraen-1-yl, cyclododeca-1,3,5,7,9-pentaen-1-yl, cyclododeca-1,3,5,7,10-pentaen-1-yl, cyclododeca-1,3,5,7,11-pentaen-1-yl, cyclododeca-1,3,5,8,10-pentaen-1-yl, cyclododeca-1,3,5,8,11-pentaen-1-yl, cyclododeca-1,3,5,9,11-pentaen-1-yl, cyclododeca-1,3,6,8,10-pentaen-1-yl, cyclododeca-1,3,6,8,11-pentaen-1-yl, cyclododeca-1,3,6,9,11-pentaen-1-yl, cyclododeca-1,3,7,9,11-pentaen-1-yl, cyclododeca-1,4,6,8,10-pentaen-1-yl, cyclododeca-1,4,6,8,11-pentaen-1-yl, cyclododeca-1,4,6,9,11-pentaen-1-yl, cyclododeca-1,4,7,9,11-pentaen-1-yl, cyclododeca-1,5,7,9,11-pen-

taen-1-yl, cyclododeca-2,4,6,8,10-pentaen-1-yl, cyclododeca-2,4,6,8,11-pentaen-1-yl, cyclododeca-2,4,6,9,11-pentaen-1-yl and cyclododeca-1,3,5,7,9,11-hexaen-1-yl.

[0110] The term "C_{13}-cycloalkenyl," as used herein, means cyclotridec-1-en-1-yl, cyclotridec-2-en-1-yl, cyclotridec-3-en-1-yl, cyclotridec-4-en-1-yl, cyclotridec-5-en-1-yl, cyclotridec-6-en-1-yl, cyclotridec-7-en-1-yl, cyclotrideca-1,3-dien-1-yl, cyclotrideca-1,4-dien-1-yl, cyclotrideca-1,5-dien-1-yl, cyclotrideca-1,6-dien-1-yl, cyclotrideca-1,7-dien-1-yl, cyclotrideca-1,8-dien-1-yl, cyclotrideca-1,9-dien-1-yl, cyclotrideca-1,10-dien-1-yl, cyclotrideca-1,11-dien-1-yl, cyclotrideca-1,12-dien-1-yl, cyclotrideca-2,4-dien-1-yl, cyclotrideca-2,5-dien-1-yl, cyclotrideca-2,6-dien-1-yl, cyclotrideca-2,7-dien-1-yl, cyclotrideca-2,8-dien-1-yl, cyclotrideca-2,9-dien-1-yl, cyclotrideca-2,10-dien-1-yl, cyclotrideca-2,11-dien-1-yl, cyclotrideca-2,12-dien-1-yl, cyclotrideca-3,5-dien-1-yl, cyclotrideca-3,6-dien-1-yl, cyclotrideca-3,7-dien-1-yl, cyclotrideca-3,8-dien-1-yl, cyclotrideca-3,9-dien-1-yl, cyclotrideca-3,10-dien-1-yl, cyclotrideca-3,11-dien-1-yl, cyclotrideca-4,6-dien-1-yl, cyclotrideca-4,7-dien-1-yl, cyclotrideca-4,8-dien-1-yl, cyclotrideca-4,9-dien-1-yl, cyclotrideca-4,10-dien-1-yl, cyclotrideca-5,7-dien-1-yl, cyclotrideca-5,8-dien-1-yl, cyclotrideca-5,9-dien-1-yl, cyclotrideca-6,8-dien-1-yl, cyclotrideca-1,3,5-trien-1-yl, cyclotrideca-1,3,6-trien-1-yl, cyclotrideca-1,3,7-trien-1-yl, cyclotrideca-1,3,8-trien-1-yl, cyclotrideca-1,3,9-trien-1-yl, cyclotrideca-1,3,10-trien-1-yl, cyclotrideca-1,3,11-trien-1-yl, cyclotrideca-1,3,12-trien-1-yl, cyclotrideca-1,4,6-trien-1-yl, cyclotrideca-1,4,7-trien-1-yl, cyclotrideca-1,4,8-trien-1-yl, cyclotrideca-1,4,9-trien-1-yl, cyclotrideca-1,4,10-trien-1-yl, cyclotrideca-1,4,11-trien-1-yl, cyclotrideca-1,4,12-trien-1-yl, cyclotrideca-1,5,7-trien-1-yl, cyclotrideca-1,5,8-trien-1-yl, cyclotrideca-1,5,9-trien-1-yl, cyclotrideca-1,5,10-trien-1-yl, cyclotrideca-1,5,11-trien-1-yl, cyclotrideca-1,5,12-trien-1-yl, cyclotrideca-1,6,8-trien-1-yl, cyclotrideca-1,6,9-trien-1-yl, cyclotrideca-1,6,10-tri-en-1-yl, cyclotrideca-1,6,11-trien-1-yl, cyclotrideca-1,6,12-trien-1-yl, cyclotrideca-1,7,9-trien-1-yl, cyclotrideca-1,7,10-trien-1-yl, cyclotrideca-1,7,11-tri-en-1-yl, cyclotrideca-1,7,12-trien-1-yl, cyclotrideca-1,8,10-trien-1-yl, cyclotrideca-1,8,11-trien-1-yl, cyclotrideca-1,8,12-trien-1-yl, cyclotrideca-1,9,11-trien-1-yl, cyclotrideca-1,9,12-trien-1-yl, cyclotrideca-1,10,12-trien-1-yl, cyclotrideca-2,4,6-trien-1-yl, cyclotrideca-2,4,7-trien-1-yl, cyclotrideca-2,4,8-trien-1-yl, cyclotrideca-2,4,9-trien-1-yl, cyclotrideca-2,4,10-trien-1-yl, cyclotrideca-2,4,11-trien-1-yl, cyclotrideca-2,4,12-trien-1-yl, cyclotrideca-2,5,7-trien-1-yl, cyclotrideca-2,5,8-trien-1-yl, cyclotri-deca-2,5,9-trien-1-yl, cyclotri-deca-2,5,10-trien-1-yl, cyclotrideca-2,5,11-trien-1-yl, cyclotrideca-2,5,12-trien-1-yl, cyclotrideca-2,6,8-trien-1-yl, cyclotrideca-2,6,9-trien-1-yl, cyclotrideca-2,6,10-trien-1-yl, cyclotrideca-2,6,11-trien-1-yl, cyclotrideca-2,6,12-trien-1-yl, cyclotrideca-2,7,9-trien-1-yl, cyclotrideca-2,7,10-trien-1-yl, cyclotrideca-2,7,11-trien-1-yl, cyclotrideca-2,7,12-trien-1-yl, cyclotrideca-2,8,10-trien-1-yl, cyclotrideca-2,8,11-trien-1-yl, cyclotrideca-2,8,12-trien-1-yl, cyclotrideca-2,9,11-trien-1-yl, cyclotrideca-2,9,12-trien-1-yl, cyclotrideca-2,10,12-trien-1-yl, cyclotrideca-3,5,7-trien-1-yl, cyclotrideca-3,5,8-trien-1-yl, cyclotrideca-3,5,9-trien-1-yl, cyclotrideca-3,5,10-trien-1-yl, cyclotrideca-3,5,11-trien-1-yl, cyclotrideca-3,6,8-trien-1-yl, cyclotrideca-3,6,9-trien-1-yl, cyclotrideca-3,6,10-trien-1-yl, cyclotrideca-3,6,11-trien-1-yl, cyclotrideca-3,7,9-trien-1-yl, cyclotrideca-3,7,10-trien-1-yl, cyclotrideca-3,7,11-tri-en-1-yl, cyclotrideca-3,8,10-trien-1-yl, cyclotrideca-4,6,8-trien-1-yl, cyclotrideca-4,6,9-trien-1-yl, cyclotrideca-4,6,10-trien-1-yl, cyclotrideca-4,7,9-trien-1-yl, cyclotrideca-4,7,10-trien-1-yl, cyclotrideca-1,3,5,7-tetraen-1-yl, cyclotrideca-1,3,5,8-tetraen-1-yl, cyclotrideca-1,3,5,9-tetraen-1-yl, cyclotrideca-1,3,5,10-tetraen-1-yl, cyclotrideca-1,3,5,11-tetraen-1-yl, cyclotrideca-1,3,5,12-tetraen-1-yl, cyclotrideca-1,3,6,8-tetraen-1-yl, cyclotrideca-1,3,6,9-tetraen-1-yl, cyclotrideca-1,3,6,10-tetraen-1-yl, cyclotrideca-1,3,6,11-tetraen-1-yl, cyclotrideca-1,3,6,12-tetraen-1-yl, cyclotrideca-1,3,7,9-tetraen-1-yl, cyclotrideca-1,3,7,10-tetraen-1-yl, cyclotrideca-1,3,7,11-tetraen-1-yl, cyclotrideca-1,3,7,12-tetraen-1-yl, cyclotri-deca-1,3,8,10-tetraen-1-yl, cyclotrideca-1,3,8,11-tetraen-1-yl, cyclotrideca-1,3,8,12-tetraen-1-yl, cyclotrideca-1,3,9,11-tetraen-1-yl, cyclotrideca-1,3,9,12-tetraen-1-yl, cyclotrideca-1,3,10,12-tetraen-1-yl, cyclotrideca-1,4,6,8-tetraen-1-yl, cyclotrideca-1,4,6,9-tetraen-1-yl, cyclotri-deca-1,4,6,10-tetraen-1-yl, cyclotrideca-1,4,6,11-tetraen-1-yl, cyclotrideca-1,4,6,12-tetraen-1-yl, cyclotrideca-1,4,7,9-tetraen-1-yl, cyclotrideca-1,4,7,10-tetraen-1-yl, cyclotrideca-1,4,7,11-tetraen-1-yl, cyclotrideca-1,4,7,12-tetraen-1-yl, cyclotri-deca-1,4,8,10-tetraen-1-yl, cyclotrideca-1,4,8,11-tetraen-1-yl, cyclotrideca-1,4,8,12-tetraen-1-yl, cyclotrideca-1,4,9,11-tetraen-1-yl, cyclotrideca-1,4,9,12-tetraen-1-yl, cyclotrideca-1,4,10,12-tetraen-1-yl, cyclotrideca-1,5,7,9-tetraen-1-yl, cyclotrideca-1,5,7,10-tetraen-1-yl, cyclotri-deca-1,5,7,11-tetraen-1-yl, cyclotrideca-1,5,7,12-tetraen-1-yl, cyclotrideca-1,5,8,10-tetraen-1-yl, cyclotrideca-1,5,8,11-tetraen-1-yl, cyclotrideca-1,5,8,12-tetraen-1-yl, cyclotrideca-1,5,9,11-tetraen-1-yl, cyclotrideca-1,5,9,12-tetraen-1-yl, cyclotrideca-1,5,10,12-tetraen-1-yl, cyclotrideca-1,6,8,10-tetraen-1-yl, cyclotri-deca-1,6,8,11-tetraen-1-yl, cyclotrideca-1,6,8,12-tetraen-1-yl, cyclotrideca-1,6,9,11-tetraen-1-yl, cyclotrideca-1,6,9,12-tetraen-1-yl, cyclotrideca-1,6,10,12-tetraen-1-yl, cyclotrideca-1,7,9,11-tetraen-1-yl, cyclotrideca-1,7,9,12-tetraen-1-yl, cyclotri-deca-1,7,10,12-tetraen-1-yl, cyclotrideca-1,8,10,12-tetraen-1-yl, cyclotrideca-2,4,6,8-tetraen-1-yl, cyclotrideca-2,4,6,9-tetraen-1-yl, cyclotrideca-2,4,6,10-tetraen-1-yl, cyclotrideca-2,4,6,11-tetraen-1-yl, cyclotrideca-2,4,6,12-tetraen-1-yl, cyclotrideca-2,4,7,9-tetraen-1-yl, cyclotri-deca-2,4,7,10-tetraen-1-yl, cyclotrideca-2,4,7,11-tetraen-1-yl, cyclotrideca-2,4,7,12-tetraen-1-yl, cyclotrideca-2,4,8,10-tetraen-1-yl, cyclotri-deca-2,4,8,11-tetraen-1-yl, cyclotrideca-2,4,8,12-tetraen-1-yl, cyclotrideca-2,4,9,11-tetraen-1-yl, cyclotrideca-2,4,9,12-tetraen-1-yl, cyclotrideca-2,4,10,12-tetraen-1-yl, cyclotrideca-2,5,7,9-tetraen-1-yl, cyclotrideca-2,5,7,10-tetraen-1-yl, cyclotrideca-2,5,7,11-tetraen-1-yl, cyclotrideca-2,5,7,12-tetraen-1-yl, cyclotrideca-2,5,8,10-tetraen-1-yl, cyclotrideca-2,5,8,11-tetraen-1-yl, cyclotrideca-2,5,8,12-tetraen-1-yl, cyclotri-deca-2,5,9,11-tetraen-1-yl, cyclotrideca-2,5,9,12-tetraen-1-yl, cyclotrideca-2,5,10,12-tetraen-1-yl, cyclotrideca-2,6,8,10-tetraen-1-yl, cyclotrideca-2,6,8,11-tetraen-1-yl, cyclotrideca-2,6,8,12-tetraen-1-yl, cyclotrideca-2,6,9,11-tetraen-1-yl, cyclotrideca-2,6,9,12-

tetraen-1-yl, cyclotri-deca-2,6,10,12-tetraen-1-yl, cyclotrideca-2,7,9,11-tetraen-1-yl, cyclotrideca-2,7,9,12-tetraen-1-yl, cyclotrideca-2,7,10,12-tetraen-1-yl, cyclotri-deca-3,5,7,9-tetraen-1-yl, cyclotrideca-3,5,7,10-tetraen-1-yl, cyclotrideca-3,5,7,11-tetraen-1-yl, cyclotrideca-3,5,8,10-tetraen-1-yl, cyclotrideca-3,5,8,11-tetraen-1-yl, cyclotrideca-3,5,9,11-tetraen-1-yl, cyclotrideca-3,6,8,10-tetraen-1-yl, cyclotrideca-3,6,8,11-tetraen-1-yl, cyclotrideca-3,7,9,11-tetraen-1-yl, cyclotrideca-1,3,5,7,9-pentaen-1-yl, cyclotrideca-1,3,5,7,10-pentaen-1-yl, cyclotrideca-1,3,5,7,11-pentaen-1-yl, cyclotrideca-1,3,5,7,12-pentaen-1-yl, cyclotrideca-1,3,5,8,10-pentaen-1-yl, cyclotrideca-1,3,5,8,11-pentaen-1-yl, cyclotrideca-1,3,5,8,12-pentaen-1-yl, cyclotrideca-1,3,5,9,11-pentaen-1-yl, cyclotrideca-1,3,5,9,12-pentaen-1-yl, cyclotrideca-1,3,6,8,10-pentaen-1-yl, cyclotrideca-1,3,6,8,11-pentaen-1-yl, cyclotrideca-1,3,6,8,12-pentaen-1-yl, cyclotrideca-1,3,6,9,11-pentaen-1-yl, cyclotrideca-1,3,6,9,12-pentaen-1-yl, cyclotrideca-1,3,7,9,11-pentaen-1-yl, cyclotrideca-1,3,7,9,12-pentaen-1-yl, cyclotrideca-1,4,6,8,10-pentaen-1-yl, cyclotrideca-1,4,6,8,11-pentaen-1-yl, cyclotrideca-1,4,6,8,12-pentaen-1-yl, cyclotrideca-1,4,6,9,11-pentaen-1-yl, cyclotrideca-1,4,6,9,12-pentaen-1-yl, cyclotrideca-1,4,7,9,11-pentaen-1-yl, cyclotrideca-1,4,7,9,12-pentaen-1-yl, cyclotrideca-1,5,7,9,11-pentaen-1-yl, cyclotrideca-1,5,7,9,12-pentaen-1-yl, cyclotrideca-2,4,6,8,10-pentaen-1-yl, cyclotrideca-2,4,6,8,11-pentaen-1-yl, cyclotrideca-2,4,6,8,12-pentaen-1-yl, cyclotrideca-2,4,6,9,11-pentaen-1-yl, cyclotrideca-2,5,7,9,11-pentaen-1-yl, cyclotrideca-2,5,7,9,12-pentaen-1-yl, cyclotrideca-1,3,5,7,9,11-hexaen-1-yl and cyclotrideca-2,4,6,8,10,12-hexaen-1-yl.

[0111] The term "C_{14}-cycloalkenyl," as used herein, means cyclotetradec-1-en-1-yl, cyclotetradec-2-en-1-yl, cyclotetradec-3-en-1-yl, cyclotetradec-4-en-1-yl, cyclotetradec-5-en-1-yl, cyclotetradec-6-en-1-yl, cyclotetradec-7-en-1-yl, cyclotetradec-8-en-1-yl, cyclotetradeca-1,3-dien-1-yl, cyclotetradeca-1,4-dien-1-yl, cyclotetradeca-1,5-dien-1-yl, cyclotetradeca-1,6-dien-1-yl, cyclotetradeca-1,7-dien-1-yl, cyclotetradeca-1,8-dien-1-yl, cyclotetradeca-1,9-dien-1-yl, cyclotetradeca-1,10-dien-1-yl, cyclotetradeca-1,11-di-en-1-yl, cyclotetradeca-1,12-dien-1-yl, cyclotetradeca-1,13-dien-1-yl, cyclotetradeca-2,4-dien-1-yl, cyclotetradeca-2,5-dien-1-yl, cyclotetradeca-2,6-dien-1-yl, cyclotetradeca-2,7-dien-1-yl, cyclotetradeca-2,8-dien-1-yl, cyclotetradeca-2,9-dien-1-yl, cyclotetradeca-2,10-dien-1-yl, cyclotetradeca-2,11-dien-1-yl, cyclotetradeca-2,12-dien-1-yl, cyclotetradeca-2,13-dien-1-yl, cyclotetradeca-3,5-dien-1-yl, cyclotetradeca-3,6-dien-1-yl, cyclotetradeca-3,7-dien-1-yl, cyclotetradeca-3,8-dien-1-yl, cyclotetradeca-3,9-dien-1-yl, cyclotetradeca-3,10-dien-1-yl, cyclotetradeca-3,11-dien-1-yl, cyclotetradeca-3,12-dien-1-yl, cyclotetradeca-4,6-dien-1-yl, cyclotetradeca-4,7-dien-1-yl, cyclotetradeca-4,8-dien-1-yl, cyclotetradeca-4,9-dien-1-yl, cyclotetradeca-4,10-dien-1-yl, cyclotetradeca-4,11-dien-1-yl, cyclotetradeca-5,7-dien-1-yl, cyclotetradeca-5,8-dien-1-yl, cyclotetradeca-5,9-dien-1-yl, cyclotetradeca-5,10-dien-1-yl, cyclotetradeca-6,8-dien-1-yl, cyclotetra-deca-6,9-dien-1-yl, cyclotetradeca-1,3,5-tetraen-1-yl, cyclotetradeca-1,3,6-tetraen-1-yl, cyclotetradeca-1,3,7-tetraen-1-yl, cyclotetradeca-1,3,8-tetraen-1-yl, cyclotetradeca-1,3,9-tetraen-1-yl, cyclotetradeca-1,3,10-tetraen-1-yl, cyclotetradeca-1,3,11-tetraen-1-yl, cyclotetradeca-1,3,12-tetraen-1-yl, cyclotetradeca-1,3,13-tetraen-1-yl, cyclotetradeca-1,4,6-tetraen-1-yl, cyclotetradeca-1,4,7-tetraen-1-yl, cyclotetradeca-1,4,8-tetraen-1-yl, cyclotetradeca-1,4,9-tetraen-1-yl, cyclotetradeca-1,4,10-tetraen-1-yl, cyclotetradeca-1,4,11-tetraen-1-yl, cyclotetradeca-1,4,12-tetraen-1-yl, cyclotetradeca-1,4,13-tetraen-1-yl, cyclotetradeca-1,5,7-tetraen-1-yl, cyclotetradeca-1,5,8-tetraen-1-yl, cyclotetradeca-1,5,9-tetraen-1-yl, cyclotetradeca-1,5,10-tetraen-1-yl, cyclotetradeca-1,5,11-tetraen-1-yl, cyclotetradeca-1,5,12-tetraen-1-yl, cyclotetradeca-1,5,13-tetraen-1-yl, cyclotetradeca-1,6,8-tetraen-1-yl, cyclotetradeca-1,6,9-tetraen-1-yl, cyclotetradeca-1,6,10-tetraen-1-yl, cyclotetradeca-1,6,11-tetraen-1-yl, cyclotetradeca-1,6,12-tetraen-1-yl, cyclotetradeca-1,6,13-tetraen-1-yl, cyclotetradeca-1,7,9-tetraen-1-yl, cyclotetradeca-1,7,10-tetraen-1-yl, cyclotetradeca-1,7,11-tetraen-1-yl, cyclotetradeca-1,7,12-tetraen-1-yl, cyclotetradeca-1,7,13-tetraen-1-yl, cyclotetradeca-1,8,10-tetraen-1-yl, cyclotetradeca-1,8,11-tetraen-1-yl, cyclotetradeca-1,8,12-tetraen-1-yl, cyclotetradeca-1,8,13-tetraen-1-yl, cyclotetradeca-1,9,11-tetraen-1-yl, cyclotetradeca-1,9,12-tetraen-1-yl, cyclotetradeca-1,9,13-tetraen-1-yl, cyclotetradeca-1,10,12-tetraen-1-yl, cyclotetradeca-1,10,13-tetraen-1-yl, cyclotetradeca-1,11,13-tetraen-1-yl, cyclotetradeca-2,4,6-tetraen-1-yl, cyclotetradeca-2,4,7-tetraen-1-yl, cyclotetradeca-2,4,8-tetraen-1-yl, cyclotetradeca-2,4,9-tetraen-1-yl, cyclotetradeca-2,4,10-tetraen-1-yl, cyclotetradeca-2,4,11-tetraen-1-yl, cyclotetradeca-2,4,12-tetraen-1-yl, cyclotetradeca-2,4,13-tetraen-1-yl, cyclotetradeca-2,5,7-tetraen-1-yl, cyclotetradeca-2,5,8-tetraen-1-yl, cyclotetradeca-2,5,9-tetraen-1-yl, cyclotetradeca-2,5,10-tetraen-1-yl, cyclotetradeca-2,5,11-tetraen-1-yl, cyclotetradeca-2,5,12-tetraen-1-yl, cyclotetradeca-2,5,13-tetraen-1-yl, cyclotetradeca-2,6,8-tetraen-1-yl, cyclotetradeca-2,6,9-tetraen-1-yl, cyclotetradeca-2,6,10-tetraen-1-yl, cyclotetradeca-2,6,11-tetraen-1-yl, cyclotetradeca-2,6,12-tetraen-1-yl, cyclotetradeca-2,6,13-tetraen-1-yl, cyclotetradeca-2,7,9-tetraen-1-yl, cyclotetradeca-2,7,10-tetraen-1-yl, cyclotetradeca-2,7,11-tetraen-1-yl, cyclotetradeca-2,7,12-tetraen-1-yl, cyclotetradeca-2,7,13-tetraen-1-yl, cyclotetradeca-2,8,10-tetraen-1-yl, cyclotetradeca-2,8,11-tetraen-1-yl, cyclotetradeca-2,8,12-tetraen-1-yl, cyclotetradeca-2,8,13-tetraen-1-yl, cyclotetradeca-2,9,11-tetraen-1-yl, cyclotetradeca-2,9,12-tetraen-1-yl, cyclotetradeca-2,9,13-tetraen-1-yl, cyclotetradeca-2,10,12-tetraen-1-yl, cyclotetradeca-2,10,13-tetraen-1-yl, cyclotetradeca-2,11,13-tetraen-1-yl, cyclotetradeca-3,5,7-tetraen-1-yl, cyclotetradeca-3,5,8-tetraen-1-yl, cyclotetradeca-3,5,9-tetraen-1-yl, cyclotetradeca-3,5,10-tetraen-1-yl, cyclotetradeca-3,5,11-tetraen-1-yl, cyclotetradeca-3,5,12-tetraen-1-yl, cyclotetradeca-3,6,8-tetraen-1-yl, cyclotetradeca-3,6,9-tetraen-1-yl, cyclotetradeca-3,6,10-tetraen-1-yl, cyclotetradeca-3,6,11-tetraen-1-yl, cyclotetradeca-3,6,12-tetraen-1-yl, cyclotetradeca-3,7,9-tetraen-1-yl, cyclotetradeca-3,7,10-tetraen-1-yl, cyclotetradeca-3,7,11-tetraen-1-yl, cyclotetradeca-3,7,12-tetraen-1-yl, cyclotetradeca-3,8,10-tetraen-1-yl, cyclotetradeca-3,8,11-tetraen-1-yl, cyclotetradeca-3,9,11-tetraen-1-yl, cyclotetradeca-4,6,8-tetraen-1-yl, cyclotetradeca-4,6,9-tetraen-1-yl, cyclotetradeca-4,6,10-tetraen-1-yl, cy-

clotetradeca-4,6,11-tetraen-1-yl, cyclotetradeca-4,7,9-tetraen-1-yl, cyclotetradeca-4,7,10-tetraen-1-yl, cyclotetradeca-4,7,11-tetraen-1-yl, cyclotetradeca-4,8,10-tetraen-1-yl, cyclotetradeca-1,3,5,7-tetraen-1-yl, cyclotetradeca-1,3,5,8-tetraen-1-yl, cyclotetradeca-1,3,5,9-tetraen-1-yl, cyclotetradeca-1,3,5,10-tetraen-1-yl, cyclotetradeca-1,3,5,11-tetraen-1-yl, cyclotetradeca-1,3,5,12-tetraen-1-yl, cyclotetradeca-1,3,5,13-tetraen-1-yl, cyclotetradeca-1,3,6,8-tetraen-1-yl, cyclotetradeca-1,3,6,9-tetraen-l-yl, cyclotetradeca-1,3,6,10-tetraen-1-yl, cyclotetradeca-1,3,6,11-tetraen-1-yl, cyclotetradeca-1,3,6,12-tetraen-1-yl, cyclotetradeca-1,3,6,13-tetraen-1-yl, cyclotetradeca-1,3,7,9-tetraen-1-yl, cyclotetradeca-1,3,7,10-tetraen-1-yl, cyclotetradeca-1,3,7,11-tetraen-1-yl, cyclotetradeca-1,3,7,12-tetraen-1-yl, cyclotetradeca-1,3,7,13-tetraen-1-yl, cyclotetradeca-1,3,8,10-tetraen-1-yl, cyclotetradeca-1,3,8,11-tetraen-1-yl, cyclotetradeca-1,3,8,12-tetraen-1-yl, cyclotetradeca-1,3,8,13-tetraen-1-yl, cyclotetradeca-1,3,9,11-tetraen-1-yl, cyclotetradeca-1,3,9,12-tetraen-1-yl, cyclotetradeca-1,3,9,13-tetraen-1-yl, cyclotetradeca-1,3,10,12-tetraen-1-yl, cyclotetradeca-1,3,10,13-tetraen-1-yl, cyclotetradeca-1,3,11,13-tetraen-1-yl, cyclotetradeca-1,4,6,8-tetraen-1-yl, cyclotetradeca-1,4,6,9-tetraen-1-yl, cyclotetradeca-1,4,6,10-tetraen-1-yl, cyclotetradeca-1,4,6,11-tetraen-1-yl, cyclotetradeca-1,4,6,12-tetraen-1-yl, cyclotetradeca-1,4,6,13-tetraen-1-yl, cyclotetradeca-1,4,7,9-tetraen-1-yl, cyclotetradeca-1,4,7,10-tetraen-1-yl, cyclotetradeca-1,4,7,11-tetraen-1-yl, cyclotetradeca-1,4,7,12-tetraen-1-yl, cyclotetradeca-1,4,7,13-tetraen-1-yl, cyclotetradeca-1,4,8,10-tetraen-1-yl, cyclotetradeca-1,4,8,11-tetraen-1-yl, cyclotetradeca-1,4,8,12-tetraen-1-yl, cyclotetradeca-1,4,8,13-tetraen-1-yl, cyclotetradeca-1,4,9,11-tetraen-1-yl, cyclotetradeca-1,4,9,12-tetraen-1-yl, cyclotetradeca-l,4,9,13-tetraen-l-yl, cyclotetradeca-1,4,10,12-tetraen-1-yl, cyclotetradeca-1,4,10,13-tetraen-1-yl, cyclotetradeca-1,4,11,13-tetraen-1-yl, cyclotetradeca-1,5,7,9-tetraen-1-yl, cyclotetradeca-1,5,7,10-tetraen-1-yl, cyclotetradeca-1,5,7,11-tetraen-1-yl, cyclotetradeca-1,5,7,12-tetraen-1-yl, cyclotetradeca-1,5,7,13-tetraen-1-yl, cyclotetradeca-1,5,8,10-tetraen-1-yl, cyclotetradeca-1,5,8,11-tetraen-1-yl, cyclotetradeca-1,5,8,12-tetraen-1-yl, cyclotetradeca-1,5,8,13-tetraen-1-yl, cyclotetradeca-1,5,9,11-tetraen-1-yl, cyclotetradeca-1,5,9,12-tetraen-1-yl, cyclotetradeca-1,5,9,13-tetraen-1-yl, cyclotetradeca-1,5,10,12-tetraen-1-yl, cyclotetradeca-1,5,10,13-tetraen-1-yl, cyclotetradeca-1,5,11,13-tetraen-1-yl, cyclotetradeca-1,6,8,10-tetraen-1-yl, cyclotetradeca-1,6,8,11-tetraen-1-yl, cyclotetradeca-1,6,8,12-tetraen-1-yl, cyclotetradeca-1,6,8,13-tetraen-1-yl, cyclotetradeca-1,6,9,11-tetraen-1-yl, cyclotetradeca-1,6,9,12-tetraen-1-yl, cyclotetradeca-1,6,9,13-tetraen-1-yl, cyclotetradeca-1,6,10,12-tetraen-1-yl, cyclotetradeca-1,6,10,13-tetraen-1-yl, cyclotetradeca-1,6,11,13-tetraen-1-yl, cyclotetradeca-1,7,9,11-tetraen-1-yl, cyclotetradeca-1,7,9,12-tetraen-1-yl, cyclotetradeca-1,7,9,13-tetraen-1-yl, cyclotetradeca-1,7,10,12-tetraen-1-yl, cyclotetradeca-1,7,10,13-tetraen-1-yl, cyclotetradeca-1,7,11,13-tetraen-1-yl, cyclotetradeca-1,8,10,12-tetraen-1-yl, cyclotetradeca-1,8,10,13-tetraen-1-yl, cyclotetradeca-1,8,11,13-tetraen-1-yl, cyclotetradeca-2,4,6,8-tetraen-1-yl, cyclotetradeca-2,4,6,9-tetraen-1-yl, cyclotetradeca-2,4,6,10-tetraen-1-yl, cyclotetradeca-2,4,6,11-tetraen-1-yl, cyclotetradeca-2,4,6,12-tetraen-1-yl, cyclotetradeca-2,4,6,13-tetraen-1-yl, cyclotetradeca-2,4,7,9-tetraen-1-yl, cyclotetradeca-2,4,7,10-tetraen-1-yl, cyclotetradeca-2,4,7,11-tetraen-1-yl, cyclotetradeca-2,4,7,12-tetraen-1-yl, cyclotetradeca-2,4,7,13-tetraen-1-yl, cyclotetradeca-2,4,8,10-tetraen-1-yl, cyclotetradeca-2,4,8,11-tetraen-1-yl, cyclotetradeca-2,4,8,12-tetraen-1-yl, cyclotetradeca-2,4,8,13-tetraen-1-yl, cyclotetradeca-2,4,9,11-tetraen-1-yl, cyclotetradeca-2,4,9,12-tetraen-1-yl, cyclotetradeca-2,4,9,13-tetraen-1-yl, cyclotetradeca-2,4,10,12-tetraen-1-yl, cyclotetradeca-2,4,10,13-tetraen-1-yl, cyclotetradeca-2,4,11,13-tetraen-1-yl, cyclotetradeca-2,5,7,9-tetraen-1-yl, cyclotetradeca-2,5,7,10-tetraen-1-yl, cyclotetradeca-2,5,7,11-tetraen-1-yl, cyclotetradeca-2,5,7,12-tetraen-1-yl, cyclotetradeca-2,5,7,13-tetraen-1-yl, cyclotetradeca-2,5,8,10-tetraen-1-yl, cyclotetradeca-2,5,8,11-tetraen-1-yl, cyclotetradeca-2,5,8,12-tetraen-1-yl, cyclotetradeca-2,5,8,13-tetraen-1-yl, cyclotetradeca-2,5,9,11-tetraen-1-yl, cyclotetradeca-2,5,9,12-tetraen-1-yl, cyclotetradeca-2,5,9,13-tetraen-1-yl, cyclotetradeca-2,5,10,12-tetraen-1-yl, cyclotetradeca-2,5,10,13-tetraen-1-yl, cyclotetradeca-2,6,8,10-tetraen-1-yl, cyclotetradeca-2,6,8,11-tetraen-1-yl, cyclotetradeca-2,6,8,12-tetraen-1-yl, cyclotetradeca-2,6,8,13-tetraen-1-yl, cyclotetradeca-2,6,9,11-tetraen-1-yl, cyclotetradeca-2,6,9,12-tetraen-1-yl, cyclotetradeca-2,6,9,13-tetraen-1-yl, cyclotetradeca-2,6,10,12-tetraen-1-yl, cyclotetradeca-2,6,10,13-tetraen-1-yl, cyclotetradeca-2,6,11,13-tetraen-1-yl, cyclotetradeca-2,7,9,11-tetraen-1-yl, cyclotetradeca-2,7,9,12-tetraen-1-yl, cyclotetradeca-2,7,10,12-tetraen-1-yl, cyclotetradeca-3,5,7,9-tetraen-l-yl, cyclotetradeca-3,5,7,10-tetraen-1-yl, cyclotetradeca-3,5,7,11-tetraen-1-yl, cyclotetradeca-3,5,7,12-tetraen-1-yl, cyclotetradeca-3,5,8,10-tetraen-1-yl, cyclotetradeca-3,5,8,11-tetraen-1-yl, cyclotetradeca-3,5,8,12-tetraen-l-yl, cyclotetradeca-3,5,9,11-tetraen-1-yl, cyclotetradeca-3,5,9,12-tetraen-1-yl, cyclotetradeca-3,5,10,12-tetraen-1-yl, cyclotetradeca-3,6,8,10-tetraen-1-yl, cyclotetradeca-3,6,8,11-tetraen-1-yl, cyclotetradeca-3,6,8,12-tetraen-1-yl, cyclotetradeca-3,7,9,11-tetraen-1-yl, cyclotetradeca-1,3,5,7,9-pentaen-1-yl, cyclotetradeca-1,3,5,7,10-pentaen-1-yl, cyclotetradeca-1,3,5,7,11-pentaen-1-yl, cyclotetradeca-1,3,5,7,12-pentaen-1-yl, , cyclotetradeca-1,3,5,7,13-pentaen-1-yl, cyclotetradeca-1,3,5,8,10-pentaen-1-yl, cyclotetradeca-1,3,5,8,11-pentaen-1-yl, cyclotetradeca-1,3,5,8,12-pentaen-1-yl, cyclotetradeca-1,3,5,8,13-pentaen-1-yl, cyclotetradeca-1,3,5,9,11-pentaen-1-yl, cyclotetradeca-1,3,5,9,12-pentaen-1-yl, cyclotetradeca-1,3,5,9,13-pentaen-1-yl, cyclotetradeca-1,3,5,10,12-pentaen-1-yl, cyclotetradeca-1,3,5,10,13-pentaen-1-yl, cyclotetradeca-1,3,5,11,13-pentaen-1-yl, cyclotetradeca-1,3,6,8,10-pentaen-1-yl, cyclotetradeca-1,3,6,8,11-pentaen-1-yl, cyclotetradeca-1,3,6,8,12-pentaen-1-yl, cyclotetradeca-1,3,6,8,13-pentaen-1-yl, cyclotetradeca-1,3,6,9,11-pentaen-1-yl, cyclotetradeca-1,3,6,9,12-pentaen-1-yl, cyclotetradeca-1,3,6,9,13-pentaen-1-yl, cyclotetradeca-1,3,7,9,11-pentaen-1-yl, cyclotetradeca-1,3,7,9,12-pentaen-1-yl, cyclotetradeca-1,3,7,9,13-pentaen-1-yl, cyclotetradeca-1,4,6,8,10-pentaen-1-yl, cyclotetra-

deca-1,4,6,8,11-pentaen-1-yl, cyclotetradeca-1,4,6,8,12-pentaen-1-yl, cyclotetradeca-1,4,6,8,13-pentaen-1-yl, cyclotetradeca-1,4,6,9,11-pentaen-1-yl, cyclotetradeca-1,4,6,9,12-pentaen-1-yl, cyclotetradeca-1,4,6,9,13-pentaen-1-yl, cyclotetradeca-1,4,7,9,11-pentaen-1-yl, cyclotetradeca-1,4,7,9,12-pentaen-1-yl, cyclotetradeca-1,4,7,9,13-pentaen-1-yl, cyclotetradeca-1,5,7,9,11-pentaen-1-yl, cyclotetradeca-1,5,7,9,12-pentaen-1-yl, cyclotetradeca-1,5,7,9,13-pentaen-1-yl, cyclotetradeca-2,4,6,8,10-pentaen-1-yl, cyclotetradeca-2,4,6,8,11-pentaen-1-yl, cyclotetradeca-2,4,6,8,12-pentaen-1-yl, cyclotetradeca-2,4,6,8,13-pentaen-1-yl, cyclotetradeca-2,4,6,9,11-pentaen-1-yl, cyclotetradeca-2,4,6,9,12-pentaen-1-yl, cyclotetradeca-2,4,6,9,13-pentaen-1-yl, cyclotetradeca-2,4,6,10,12-pentaen-1-yl, cyclotetradeca-2,4,6,10,13-pentaen-1-yl, cyclotetradeca-2,4,6,11,13-pentaen-1-yl, cyclotetradeca-2,4,7,9,11-pentaen-1-yl, cyclotetradeca-2,4,7,9,12-pentaen-1-yl, cyclotetradeca-2,4,7,9,13-pentaen-1-yl, cyclotetradeca-2,4,7,10,12-pentaen-1-yl, cyclotetradeca-2,4,7,10,13-pentaen-1-yl, cyclotetradeca-2,4,7,11,13-pentaen-1-yl, cyclotetradeca-2,4,8,10,12-pentaen-1-yl, cyclotetradeca-2,4,8,10,13-pentaen-1-yl, cyclotetradeca-2,5,7,9,11-pentaen-1-yl, cyclotetradeca-2,5,7,9,12-pentaen-1-yl, cyclotetradeca-2,5,7,9,13-pentaen-1-yl, cyclotetradeca-2,5,7,10,12-pentaen-1-yl, cyclotetradeca-2,5,7,10,13-pentaen-l-yl, cyclotetradeca-1,3,5,7,9,11-hexaen-1-yl, cyclotetradeca-1,3,5,7,9,12-hexaen-1-yl, cyclotetradeca-1,3,5,7,9,13-hexaen-1-yl, cyclotetradeca-2,4,6,8,10,12-hexaen-1-yl, cyclotetradeca-2,4,6,8,10,13-hexaen-1-yl, cyclotetradeca-2,4,6,8,11,13-hexaen-1-yl and cyclotetradeca-1,3,5,7,9,11,13-heptaen-1-yl.

[0112] The term "C_3-cycloalkyl," as used herein, means cycloprop-1-yl.

[0113] The term "C_4-cycloalkyl," as used herein, means cyclobut-1-yl.

[0114] The term "C_5-cycloalkyl," as used herein, means cyclopent-1-yl.

[0115] The term "C_6-cycloalkyl," as used herein, means cyclohex-1-yl.

[0116] The term "C_7-cycloalkyl," as used herein, means bicyclo[2.2.1]hept-1-yl, bicyclo[2.2.1]hept-2-yl, cyclohept-1-yl, bicyclo[2.2.1]hept-7-yl and cyclohept-1-yl.

[0117] The term "C_8-cycloalkyl," as used herein, means bicyclo[2.2.2]oct-1-yl, bicyclo[2.2.2]oct-2-yl, bicyclo[2.2.2]oct-7-yl, cyclooct-1-yl.

[0118] The term "C_9-cycloalkyl," as used herein, means cyclonon-1-yl.

[0119] The term "C_{10}-cycloalkyl," as used herein, means adamant-1-yl, adamant-2-yl and cyclodec-1-yl.

[0120] The term "C_{11}-cycloalkyl," as used herein, means cycloundec-1-yl, tricyclo[4.3.1.$1^{3,8}$]undec-1-yl (homoadamant-1-yl), tricyclo[4.3.1.$1^{3,8}$]undec-2-yl (homoadamant-2-yl), tricyclo[4.3.1.13'8]undec-3-yl (homoadamant-3-yl), $_t$ricyclo[4.3.1.13'8]undec-4-yl (homoadamant-4-yl), and tricyclo[4.3.1.$1^{3,8}$]undec-9-yl (homoadamant-9-yl).

[0121] The term "C_{12}-cycloalkyl," as used herein, means cyclododec-1-yl.

[0122] The term "C_{13}-cycloalkyl," as used herein, means cyclotridec-1-yl.

[0123] The term "C_{14}-cycloalkyl," as used herein, means cyclotetradec-1-yl.

[0124] The term "C_2-spiroalkenyl," as used herein, means ethen-1,2-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0125] The term "C_3-spiroalkenyl," as used herein, means prop-1-en-1,3-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0126] The term "C_4-spiroalkenyl," as used herein, means but-1-en-1,4-ylene, but-2-en-1,4-ylene and buta-1,3-dien-1,4-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0127] The term "C_5-spiroalkenyl," as used herein, means pent-1-en-1,5-yl-ene, pent-2-en-1,5-ylene, penta-1,3-dien-1,5-ylene and penta-1,4-dien-1,5-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0128] The term "C_6-spiroalkenyl," as used herein, means hex-1-en-1,6-ylene, hex-2-en-l,6-ylene, hexa-1,3-dien-1,6-ylene, hexa-1,4-di-en-1,6-ylene and hexa-1,3,5-trien-1,6-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0129] The term "C_7-spiroalkenyl," as used herein, means hept-1-en-1,7-yl-ene, hept-2-en-1,7-ylene, hept-3-en-1,7-ylene, hepta-1,3-dien-1,7-ylene, hepta-1,4-dien-1,7-ylene, hepta-1,5-dien-1,7-ylene, hepta-2,4-dien-1,7- ylene, hepta-2,5-dien-1,7-ylene, hepta-1,3,5-trien-1,7-ylene and hepta-1,3,6-trien-1,7-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0130] The term "C_8-spiroalkenyl," as used herein, means oct-1-en-1,8-ylene, oct-2-en-1,8-ylene, oct-3-en-1,8-ylene, octa-1,3-dien-1,8-ylene, octa-1,4-dien-1,8-ylene, octa-1,5-dien-1,8-ylene, octa-1,6-dien-1,8-ylene, octa-2,4-dien-1,8-ylene, octa-2,5-dien-1,8-ylene, octa-3,5-dien-1,8-ylene, octa-1,3,5-trien-1,8-ylene, octa-1,3,6-trien-1,8-ylene and octa-2,4,6-tri-en-1,8-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0131] The term "C_9-spiroalkenyl," as used herein, means nona-1-en-1,9-yl-ene, nona-2-en-1,9-ylene, nona-3-en-1,9-ylene, nona-4-en-1,9-ylene, nona-1,3-dien-1,9-ylene, nona-1,4-dien-1,9-ylene, nona-1,5-dien-1,9-ylene, nona-1,6-dien-1,9-ylene, nona-1,7-dien-1,9-ylene, nona-1,8-dien-1,9-ylene, nona-2,4-dien-1,9-ylene, nona-2,5-dien-1,9-ylene, nona-2,6-dien-1,9-ylene, nona-2,7-dien-1,9-ylene, nona-3,5-dien-1,9-ylene, nona-3,6-dien-1,9-ylene, nona-4,6-dien-1,9-ylene, nona-1,3,5-trien-1,9-ylene, nona-1,3,6-trien-1,9-ylene, nona-1,3,7-trien-1,9-ylene, nona-1,3,8-trien-1,9-ylene, nona-1,4,6-trien-1,9-yl-ene, nona-1,4,7-trien-1,9-ylene, nona-1,4,8-trien-1,9-ylene, nona-1,5,7-trien-1,9-ylene, nona-2,4,6-trien-1,9-ylene, nona-2,4,7-trien-1,9-ylene, nona-1,3,5,7-tetraen-1,9-ylene, nona-1,3,5,8-tetraen-1,9-ylene and nona-1,3,6,9-tetraen-1,9-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0132] The term "C_2-spiroalkyl," as used herein, means eth-1,2-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0133] The term "C_3-spiroalkyl," as used herein, means prop-1,3-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0134] The term "C_4-spiroalkyl," as used herein, means but-1,4-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0135] The term "C_5-spiroalkyl," as used herein, means pent-1,5-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0136] The term "C_6-spiroalkyl," as used herein, means hex-1,6-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0137] The term "C_7-spiroalkyl," as used herein, means hept-1,7-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0138] The term "C_8-spiroalkyl," as used herein, means oct-1,8-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0139] The term "C_9-spiroalkyl," as used herein, means non-1,9-ylene, both ends of which replace hydrogen atoms of the same CH_2 moiety.

[0140] Compounds of this invention contain asymmetrically substituted carbon atoms in the R or S configuration, in which the terms "R" and "S" are as defined by the IUPAC 1974 Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem. (1976) 45, 13-10. Compounds having asymmetrically substituted carbon atoms with equal amounts of R and S configurations are racemic at those carbon atoms. Atoms with an excess of one configuration over the other are assigned the configuration present in the higher amount, preferably an excess of about 85%-90%, more preferably an excess of about 95%-99%, and still more preferably an excess greater than about 99%. Accordingly, this invention includes racemic mixtures, relative and absolute stereoisomers, and mixtures of relative and absolute stereoisomers.

[0141] Compounds of this invention may also contain carbon-carbon double bonds or carbon-nitrogen double bonds in the Z or E configuration, in which the term "Z" represents the larger two substituents on the same side of a carbon-carbon or carbon-nitrogen double bond and the term "E" represents the larger two substituents on opposite sides of a carbon-carbon or carbon-nitrogen double bond. The compounds may also exist as an equilibrium mixture of Z or E configurations.

[0142] Compounds of this invention containing NH, C(O)OH, OH or SH moieties may have attached thereto prodrug-forming moieties. The prodrug-forming moieties are removed by metabolic processes and release the compounds having the freed hydroxyl, amino or carboxylic acid in vivo. Prodrugs are useful for adjusting such pharmacokinetic properties of the compounds as solubility and/or hydrophobicity, absorption in the gastrointestinal tract, bioavailability, tissue penetration, and rate of clearance.

[0143] Metabolites of compounds having formula (I), produced by in vitro or in vivo metabolic processes, may also have utility for treating diseases associated with expression of an anti-apoptotic protein family member such as of BC1-X_L protein, and Bcl-2 protein or Bcl-w protein.

[0144] Certain precursor compounds which may be metabolized in vitro or in vivo to form compounds having formula (I) may also have utility for treating diseases associated with expression of an anti-apoptotic protein family member such as of BC1-X_L protein, and Bcl-2 protein or Bcl-w protein.

[0145] Compounds having formula (I) may exist as an acid addition salts, basic addition salts or zwitterions. Salts of the compounds are prepared during their isolation or following their purification. Acid addition salts of the compounds are those derived from the reaction of the compounds with an acid. For example, the acetate, adipate, alginate, bicarbonate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, formate, fumarate, glycerophosphate, glutamate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactobionate, lactate, maleate, mesitylenesulfonate, methanesulfonate, naphthylenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, phosphate, picrate, propionate, succinate, tartrate, thiocyanate, trichloroacetic, trifluoroacetic, para-toluenesulfonate, and undecanoate salts of the compounds and prodrugs thereof are contemplated as being embraced by this invention. Basic addition salts of the compounds are those derived from the reaction of the compounds with the hydroxide, carbonate or bicarbonate of cations such as lithium, sodium, potassium, calcium, and magnesium.

[0146] The compounds having formula (I) may be administered, for example, bucally, ophthalmically, orally, osmotically, parenterally (intramuscularly, intraperintoneally intrasternally, intravenously, subcutaneously), rectally, topically, transdermally, or vaginally.

[0147] Therapeutically effective amounts of compounds having formula (I) depend on recipient of treatment, disorder being treated and severity thereof, composition containing it, time of administration, route of administration, duration of treatment, its potency, its rate of clearance and whether or not another drug is co-administered. The amount of a compound of this invention having formula (I) used to make a composition to be administered daily to a patient in a

single dose or in divided doses is from about 0.03 to about 200 mg/kg body weight. Single dose compositions contain these amounts or a combination of submultiples thereof.

[0148] Compounds having formula (I) may be administered with or without an excipient. Excipients include, for example, encapsulating materials or additives such as absorption accelerators, antioxidants, binders, buffers, coating agents, coloring agents, diluents, disintegrating agents, emulsifiers, extenders, fillers, flavoring agents, humectants, lubricants, perfumes, preservatives, propellants, releasing agents, sterilizing agents, sweeteners, solubilizers, wetting agents and mixtures thereof.

[0149] Excipients for preparation of compositions comprising a compound having formula (I) to be administered orally in solid dosage form include, for example, agar, alginic acid, aluminum hydroxide, benzyl alcohol, benzyl benzoate, 1,3-butylene glycol, carbomers, castor oil, cellulose, cellulose acetate, cocoa butter, corn starch, corn oil, cottonseed oil, cross-povidone, diglycerides, ethanol, ethyl cellulose, ethyl laureate, ethyl oleate, fatty acid esters, gelatin, germ oil, glucose, glycerol, groundnut oil, hydroxypropylmethyl celluose, isopropanol, isotonic saline, lactose, magnesium hydroxide, magnesium stearate, malt, mannitol, monoglycerides, olive oil, peanut oil, potassium phosphate salts, potato starch, povidone, propylene glycol, Ringer's solution, safflower oil, sesame oil, sodium carboxymethyl cellulose, sodium phosphate salts, sodium lauryl sulfate, sodium sorbitol, soybean oil, stearic acids, stearyl fumarate, sucrose, surfactants, talc, tragacanth, tetrahydrofurfuryl alcohol, triglycerides, water, and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having formula (I) to be administered ophthalmically or orally in liquid dosage forms include, for example, 1,3-butylene glycol, castor oil, corn oil, cottonseed oil, ethanol, fatty acid esters of sorbitan, germ oil, groundnut oil, glycerol, isopropanol, olive oil, polyethylene glycols, propylene glycol, sesame oil, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having formula (I) to be administered osmotically include, for example, chlorofluorohydrocarbons, ethanol, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having formula (I) to be administered parenterally include, for example, 1,3-butanediol, castor oil, corn oil, cottonseed oil, dextrose, germ oil, groundnut oil, liposomes, oleic acid, olive oil, peanut oil, Ringer's solution, safflower oil, sesame oil, soybean oil, U.S.P. or isotonic sodium chloride solution, water and mixtures thereof. Excipients for preparation of compositions comprising a compound of this invention having formula (I) to be administered rectally or vaginally include, for example, cocoa butter, polyethylene glycol, wax and mixtures thereof.

[0150] Compounds having formula (I) may also be administered with one or more than one additional therapeutic agents, wherein additional therapeutic agents include radiation or chemotherapeutic agents, wherein chemotherapeutic agents include, but are not limited to, carboplatin, cisplatin, cyclophosphamide, dacarbazine, dexamethasone, docetaxel, doxorubicin, etoposide, fludarabine, irinotecan, CHOP (C: Cytoxan® (cyclophosphamide); H: Adiamycin® (hydroxydoxorubicin); O: Vincristine (Oncovin®); P: prednisone), paclitaxel, rapamycin, Rituxin® (rituximab) and vincristine.

[0151] For determination of the utility of compounds having formula (I) as inhibitors of the activity of anti-apoptotic Bcl-X_L, representative examples in DMSO at concentrations between 100 μM and 1 pM and added to each well of a 96-well microtiter plate. A mixture totaling 125 μL per well of assay buffer (20 mM phosphate buffer, pH 7.4), 1 mM EDTA, 50 mM NaCl, 0.05% PF-68), 30 nM Bcl-X_L protein (prepared as described in Science 1997, 275, 983-986), 15 nM fluorescein-labeled BAD peptide (prepared in-house), and the DMSO solution of the example was shaken for 2 minutes then placed in a LJL Analyst (LJL Bio Systems, CA). A negative control (DMSO, 15 nM BAD peptide, assay buffer) and a positive control (DMSO, 15 nM BAD peptide, 30 nM Bcl-X_L, assay buffer) were used to determine the range of the assay. Polarization was measured at 25°C with a continuous Fluorescein lamp (excitation 485 nm; emission 530 nm). Percentage of inhibition was determined by (1-((mP value of well-negative control)/range))×100%.

[0152] IC_{50} values (concentration of example needed for 50% inhibition of Bcl-X_L) for the representative compounds having formula (I), calculated using Microsoft Excel, were 3.7 nM, 5.8 nM, 6.1 nM, 6.2 nM, 6.9 nM, 7.1 nM, 7.1 nM, 7.4 nM, 7.7 nM, 7.8 nM, 7.9 nM, 8.3 nM, 8.3 nM, 8.3 nM, 8.4 nM, 8.4 nM, 8.5 nM, 8.5 nM, 8.7 nM, 8.8 nM, 9.1 nM, 9.1 nM, 9.1 nM, 9.2 nM, 9.5 nM, 9.6 nM, 9.7 nM, 9.8 nM, 9.8 nM, 9.9 nM, 9.9 nM, 9.9 nM, 10.0 nM, 10.0 nM, 10.0 nM, 10.0 nM, 10.1 nM, 10.1 nM, 10.2 nM, 10.2 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.3 nM, 10.5 nM, 10.6 nM, 10.6 nM, 10.6 nM, 10.6 nM, 10.6 nM, 10.7 nM, 10.7 nM, 10.7 nM, 10.7 nM, 10.8 nM, 10.8 nM, 10.8 nM, 10.8 nM, 10.9 nM, 10.9 nM, 10.9 nM, 10.9 nM, 11.0 nM, 11.0 nM, 11.0 nM, 11.0 nM, 11.0 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.1 nM, 11.2 nM, 11.2 nM, 11.2 nM, 11.2 nM, 11.2 nM, 11.2 nM, 11.2 nM, 11.3 nM, 11.3 nM, 11.3 nM, 11.3 nM, 11.4 nM, 11.5 nM, 11.5 nM, 11.5 nM, 11.5 nM, 11.5 nM, 11.6 nM, 11.6 nM, 11.6 nM, 11.6 nM, 11.6 nM, 11.6 nM, 11.6 nM, 11.7 nM, 11.7 nM, 11.8 nM, 11.8 nM, 11.9 nM, 11.9 nM, 11.9 nM, 11.9 nM, 11.9 nM, 12.1 nM, 12.1 nM, 12.1 nM, 12.2 nM, 12.2 nM, 12.3 nM, 12.3 nM, 12.3 nM, 12.3 nM, 12.4 nM, 12.4 nM, 12.4 nM, 12.4 nM, 12.5 nM, 12.5 nM, 12.5 nM, 12.6 nM, 12.6 nM, 12.6 nM, 12.6 nM, 12.6 nM, 12.7 nM, 12.7 nM, 12.7 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.8 nM, 12.9 nM, 12.9 nM, 12.9 nM, 12.9 nM, 13.0 nM, 13.0 nM, 13.1 nM, 13.2 nM, 13.2 nM, 13.2 nM, 13.3 nM, 13.3 nM, 13.4 nM, 13.4 nM, 13.5 nM, 13.5 nM, 13.5 nM, 13.6 nM, 13.6 nM, 13.6 nM, 13.7 nM, 13.7 nM, 13.7 nM, 13.7 nM, 13.7 nM, 13.7 nM, 13.8 nM, 13.8 nM, 13.8 nM, 13.8 nM, 13.9 nM 13.9 nM, 13.9 nM, 13.9 nM, 13.9 nM, 13.9 nM, 13.9 nM, 14.0 nM, 14.0 nM, 14.0 nM, 14.0 nM, 14.1 nM, 14.1 nM, 14.1 nM, 14.1 nM, 14.2 nM, 14.2 nM, 14.2 nM, 14.3 nM, 14.3 nM, 14.4 nM, 14.4 nM, 14.4 nM, 14.5

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[0153] Determination of the utility of compounds having formula (I) as inhibitiors of anti-apoptotic Bcl-2 was also performed in 96-well microtiter plates. Representative examples were diluted in DMSO to concentrations between 10 μM and 10 pM and added to each well of the plate. A mixture totaling 125 μL per well of assay buffer (20 mM phosphate buffer, pH 7.4), 1 mM EDTA, 50 mM NaCl, 0.05% PF-68), 10 nM Bcl-2 protein (prepared as described in PNAS 2001, 98, 3012-3017), 1 nM fluorescein-labeled BAX peptide (prepared in-house), and the DMSO solution of the example was shaken for 2 minutes and placed in the LJL Analyst. Polarization was measured at 25°C using a continuous Fluorescein lamp (excitation 485nm; emission 530nm).

[0154] K_i values for the representative compounds having formula (I), calculated using Microsoft Excel, were <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, <1.0 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.1 nM, 1.2 nM, 1.2 nM, 1.3 nM, 1.3 nM, 1.3 nM, 1.3 nM, 1.3 nM, 1.4 nM, 1.5 nM, 1.5 nM, 1.5 nM, 1.5 nM, 1.6 nM, 1.6 nM, 1.7 nM, 1.7 nM, 1.7 nM, 1.7 nM, 1.8 nM, 1.8 nM, 1.8 nM, 1.8 nM, 1.9 nM, 2.0 nM, 2.0 nM, 2.2 nM, 2.3 nM, 2.4 nM, 2.5 nM, 2.5 nM, 2.6 nM, 2.6 nM, 2.9 nM, 3.0 nM, 3.1 nM, 3.5 nM,

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[0155] These binding and inhibitory data demonstrate the utility of compounds having formula (I) as inhibitors of anti-apopotic BC1-X_L protein and anti-apopotic Bcl-2.

[0156] It is expected that, because compounds having formula (I) bind to and inhibit the activity of BC1-X_L and Bcl-2, they would also have utility as inhibitors of anti-apopotic protein family members having close structural homology to BC1-X_L and Bcl-2, such as, for example, anti-apopotic Bcl-w protein.

[0157] Accordingly, compounds having formula (I) are expected to have utility in treatment of diseases during which anti-apopotic Bcl-X_L protein, anti-apopotic Bcl-2 protein, anti-apopotic Bcl-w protein or a combination thereof, are expressed.

[0158] Diseases during which anti-apopotic protein family members such as BC1-X_L protein, Bcl-2 protein and Bcl-w protein are expressed include cancer and autoimmune disorders, wherein cancer includes, but is not limited to, bladder cancer, brain cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer and small cell lung cancer (Cancer Res., 2000, 60, 6101-10); autoimmune disorders include, but are not limited to, acquired immunodeficiency disease syndrome, autoimmune lymphoproliferative syndrome, hemolytic anemia, inflammatory diseases, and thrombocytopenia (Current Allergy and Asthma Reports 2003, 3:378-384; Br. J. Haematol. 2000 Sep; 110(3): 584-90; Blood 2000 Feb 15;95(4):1283-92; and New England Journal of Medicine 2004 Sep; 351(14): 1409-1418).

[0159] A representative compound having formula (I), EXAMPLE 2, displayed therapeutic utility against human tumor cell lines derived from small cell lung carcinomas and lymphoid malignancies of both T-cell and B-cell origin.

[0160] EXAMPLE 2 also displayed therapeutic utility against acute lymphoblastoid leukemia, small cell lung cancer, prostate cancer, non-small cell lung cancer, and follicular lymphoma tumors (RS11380, DoHH2 and SuDHL-4) in xenograft models.

[0161] EXAMPLE 2 also demonstrated anti-tumor activity in two murine models (H146 and SCLC xenograft) from human-derived small cell lung cancer isolated from smokers and nonsmokers, defective for Rb/p53 gene function, and expresseive of moderately high levels of Bcl-2. In the H146 model, treatment with EXAMPLE 2 resulted in complete regression of an established tumor with, in some cases, tumor disappearance after prolonged therapy.

[0162] EXAMPLE 2 also prolonged survival in a systemic model of acute lymphoblastic leukemia and inhibited tumor growth in a model of follicular lymphoma (DOHH-2). Therapeutic utility was also observed in a prostate cancer model.

[0163] Without being limited by theory, the genetic link between Bcl-2 and cancer comes from the observation that t(14;18) chromosomal translocations in B-cell lymphomas lead to overexpression of the protein. Aberrant Bcl-2 and Bcl-X_L expression is also seen in other lymphoid malignancies such as chronic lymphocytic leukemia and acute lymphocytic leukemia. EXAMPLE 2 exhibited significant activity in a CCRF-CEM T-cell acute lymphoblastoid leukemia model as well as in SuDHL4 and RS11380, two models of B-cell follicular lymphoma.

[0164] CCRF-CEM is a p53-mutant acute lympoblastoid leukemia line of T-cell origin used as an animal (mouse) model of systemic leukemia involving intravenous inoculation of tumor cells. If left untreated, the mice succumb to disease within about 34 days post inoculation, at which time extensive tumor infiltration of spleen, liver, and bone marrow has occured. Administeration of EXAMPLE 2 increased the average survival of the mice and showed a significant decrease in average spleen weight relative to vehicle controls (indicative of a lower tumor burden in this organ). Subsequent histopahtological assessments revealed lower tumor infiltration in both the liver and spleen relative to controls.

[0165] The therapeutic effect of EXAMPLE 2 on other human tumor cell lines is shown in TABLE 1 for which the EC_{50}'s are the effective concentrations which cause a 50% reduction in cell viability.

TABLE 1

Cell Line[a]	Tumor Type	EC_{50} (uM)[b]
Calu-6	Non-Small Cell Lung	0.18 ± 0.07(6)
NCI-H460	Non-Small Cell Lung	2.3 ± 1.5(6)
NCI-H226	Non-Small Cell Lung	2.6 ± 1.1(2)
NCI-H322M	Non-Small Cell Lung	4.1 ± 0.8(2)
A549/ATCC	Non-Small Cell Lung	5.2 ± 0.2(2)
HOP-62	Non-Small Cell Lung	6.3 ± 6.7(2)

(continued)

Cell Line[a]	Tumor Type	EC_{50} (uM)[b]
NCI-H23	Non-Small Cell Lung	7.4 ± 0.6(2)
COLO 205	Colorectal	0.51 ± 0.07(4)
HCT-15	Colorectal	0.60 ± 0.34(4)
HCT-15	Colorectal	>11 (2)
SW-620	Colorectal	0.69 ± 0.07(2)
DLD-1	Colorectal	0.99 ± 0.45(4)
HT-29	Colorectal	1.1 ± 1.1(6)
KM12	Colorectal	1.7 ± 0.2(2)
HCT-116	Colorectal	2.1 ± 1.8(6)
MCF7	Breast	2.0 ± 0.8(2)
MDA-MB-435	Breast	2.4 (1)
MDA-MB-436	Breast	3.9 ± 2.6(2)
BT-549	Breast	6.5 ± 2.3(2)
HS-578T	Breast	7.2 ± 8.2(2)
T47D	Breast	>10(2)
NCI/ADR-RES	Breast	>10(2)
U251	CNS	3.8 ± 2.0(2)
SF-539	CNS	4.1 ± 0.6(2)
SF-295	CNS	7.7 ± 2.3(2)
SF-268	CNS	8.3 ± 0.4(2)
U87MG	Glioma	2.7 ± 1.8(2)
D54MG	Glioma	3.1 ± 2.5(2)
LOX IMVI	Melanoma	1.7 ± 0.4(2)
MALME-3M	Melanoma	1.9 ± 0.8(2)
SK-MEL-5	Melanoma	3.7 ± 0.8(2)
SK-MEL-28	Melanoma	9.3 ± 0.1(2)
OVCAR-5	Ovarian	1.1 ± 0(2)
IGROV-1	Ovarian	1.7 ± 0.6(2)
OVCAR-3	Ovarian	1.9 ± 0.3(2)
OVCAR-8	Ovarian	3.4 ± 0.8(2)
SK-OV-3	Ovarian	5.6 ± 1.0(2)
OVCAR-4	Ovarian	22 ± 3 (2)
MiaPaCa	Pancreas	1.4 ± 0.6(2)
PC3	Prostate	0.96 ± 0.38(4)
DU-145	Prostate	8.2 ± 1.1(2)
ACHN	Renal	1(1)
786-0	Renal	2.9 ± 0.1(2)
RXF-393	Renal	2.9 ± 0.4(2)
SN12C	Renal	3.2 ± 0.2(2)

[a]Serum-free conditions, 48 hour treatment.
[b]Mean ± SEM(n).

[0166] The therapeutic effect of paclitaxel on A549 human non-small cell lung carcinoma cells was about 4.4-fold more efficacious when administered with EXAMPLE 2. A similar increase (4.7-fold) in efficacy was demonstrated against PC-3 prostate carcinoma cells. The enantiomer of EXAMPLE 2 was less efficacious, indicating that the therapeutic effect of EXAMPLE 2 was the direct result of binding to anti-apoptotic Bcl-2 family proteins. The anti-tumor activity of EXAMPLE 2 was equivalent to slightly better than paclitaxel near the maximum tolerated dose in a small cell lung cancer xenograft tumor model and superior to cisplatin and etoposide. In a PC3 derived murine model of prostate cancer, EXAMPLE 2 exhibited about 40-50% inhibition of tumor growth rate.

[0167] Studies pertaining to the efficacy of EXAMPLE 2 in combination with etoposide, vincristine, modified CHOP,

doxorubicin, rapamycin and Rituxin® demonstrated that EXAMPLE 2 synergistically enhanced efficacy of these cytotoxic agents during combination therapy. In particular, combinations ocomprising EXAMPLE 2 and rapamycin and EXAMPLE 2 and Rituxin® resulted in complete regression of a significant percentage of established DoHH2 follicular lymphoma flank tumors for a sustained period of time.

[0168] These data demonstrate the utility of compounds having formula (I) for treatment of diseases which are caused or exascerbated by expression of one or more than one of an anti-apoptotic protein family member. Furthermore, experiments with representative Bcl-X_L-selective compounds demonstrated synergistic therapeutic effects with multiple chemotherapeutic agents against cell lines representative of diverse tumor types. Accordingly, the compounds having formula (I) are expected to be useful as chemotherapeutic agents alone or in combination with additional therapeutic agents.

[0169] Compounds having formula (I) may be made by synthetic chemical processes, examples of which are shown herein. It is meant to be understood that the order of the steps in the processes may be varied, reagents, solvents, and reaction conditions may be substituted for those specifically mentioned, and vulnerable moieties may be protected and deprotected, as necessary, by NH, C(O)OH, OH, SH protecting groups.

[0170] The following abbraviations have the meanings indicated. ADDP means 1,1'-(azodicarbonyl)dipiperidine; AD-mix-β means a mixture of $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, and K_2SO_4) ; 9-BBN means 9-borabicyclo[3.3.1]nonane; Boc means tert-butoxycarbonyl; $(DHQD)_2PHAL$ means hydroquinidine 1,4-phthalazinediyl diethyl ether; DBU means 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL means diisobutylaluminum hydride; DIEA means diisopropylethylamine; DMAP means N,N-dimethylaminopyridine; DMF means N,N-dimethylformamide; dmpe means 1,2-bis(dimethylphosphino)ethane; DMSO means dimethylsulfoxide; dppb means 1,4-bis(diphenylphosphino)-butane; dppe means 1,2-bis(diphenylphosphino)ethane; dppf means 1,1'-bis(diphenylphosphino)ferrocene; dppm means 1,1-bis(diphenylphosphino)methane; EDAC·HCl means 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; Fmoc means fluorenylmethoxycarbonyl; HATU means 0-(7-azabenzotriazol-1-yl)-N,N'N'N'-tetramethyluronium hexafluorophosphate; HMPA means hexamethylphosphoramide; IPA means isopropyl alcohol; MP-BH_3 means macroporus triethylammonium methylpolystyrene cyanoborohydride; TEA means triethylamine; TFA means trifluoroacetic acid; THF means tetrahydrofuran; NCS means N-chlorosuccinimide; NMM means N-methylmorpholine; NMP means N-methylpyrrolidine; PPh_3 means triphenylphosphine.

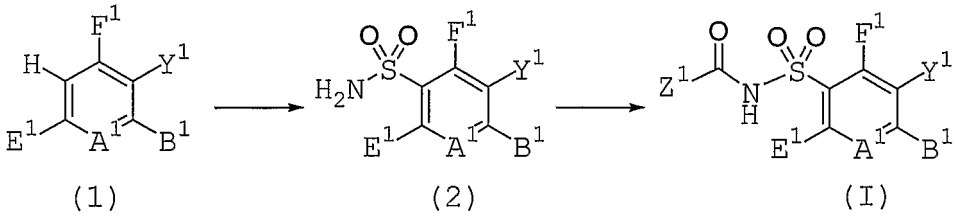
[0171] The term "NH protecting group," as used herein, means trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, para-nitrobenzylcarbonyl, ortho-bromobenzyloxycarbonyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyloxycarbonyl, tert-butoxycarbonyl, para-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)benzyloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl, benzyl, diphenylmethyl, triphenylmethyl, 2-nitrophenylthio, methanesulfonyl, para-toluenesulfonyl, N,N-dimethylaminomethylene, benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthyl-methylene, 3-hydroxy-4-pyridylmethylene, cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclohexylidene, diphenylphosphoryl, dibenzylphosphoryl, 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl, trimethylsilyl, triethylsilyl, and triphenylsilyl.

[0172] The term "C(O)OH protecting group," as used herein, means methyl, ethyl, n-propyl, isopropyl, 1,1-dimethylpropyl, n-butyl, tert-butyl, phenyl, naphthyl, benzyl, diphenylmethyl, triphenylmethyl, para-nitrobenzyl, para-methoxybenzyl, bis(para-methoxyphenyl)methyl, acetylmethyl, benzoylmethyl, para-nitrobenzoylmethyl, para-bromobenzoylmethyl, paramethanesulfonylbenzoylmethyl, 2-tetrahydropyranyl 2-tetrahydrofuranyl, 2,2,2-trichloro-ethyl, 2-(trimethylsilyl)ethyl, acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl, phthalimidomethyl, succinimidomethyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, benzyloxymethyl, methylthiomethyl, 2-methylthioethyl, phenylthiomethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-butylmethoxyphenylsilyl.

[0173] The term "OH or SH protecting group," as used herein, means benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl, vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl, methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl, benzyl (phenylmethyl), para-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, triphenylmethyl, tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl, methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl, methanesulfonyl, para-toluenesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, and tert-

butylmethoxyphenylsilyl.

SCHEME 1



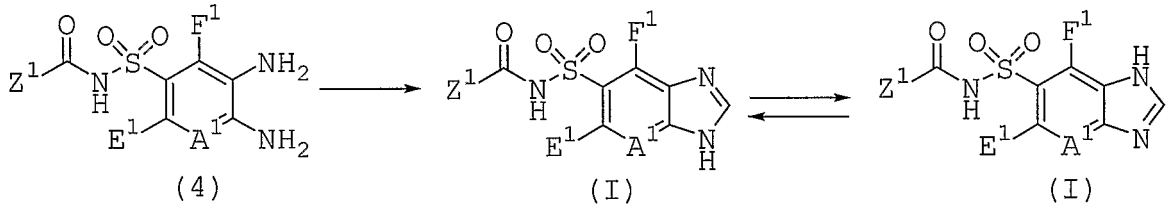
(1) (2) (I)

[0174] Compounds having formula (1) may be converted to compounds having formula (2) by reacting the former, chlorosulfonic acid, and ammonia.

[0175] Compounds having formula (2) may be converted to compounds having formula (I) by reacting the former and compounds having formula Z^1-CO_2H and a coupling agent, with or without a first base. Examples of coupling agents include EDCI, CDI, and PyBop. Examples of first bases include TEA, DIEA, DMAP, and mixtures thereof.

[0176] Compounds having formula (2) may be converted to compounds having formula (I) by reacting the former and compounds having formula Z^1-COCl and the first base.

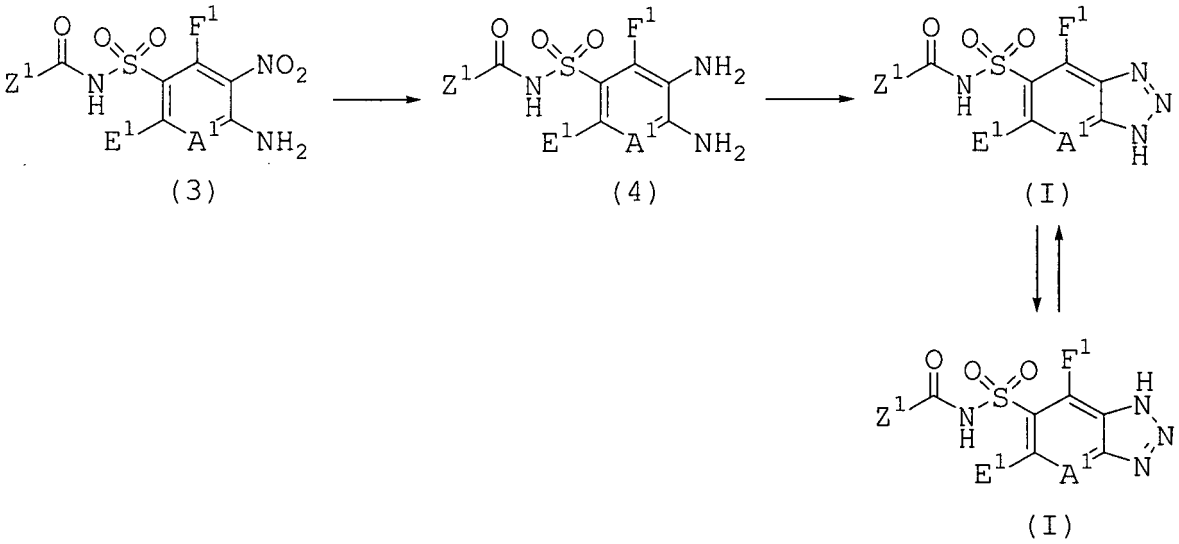
SCHEME 2



(4) (I) (I)

[0177] Compounds having formula (4) may be converted to compounds having formula (I), wherein B^1 and Y^1 together are imidazole, by reacting the former, sodium nitrite, hydrochloric acid, and acetic acid. Compounds having formula (I), wherein B^1 and Y^1 together are imidazole, may be reacted with a second base and the appropriate electrophile to provide compounds having formula (I), wherein B^1 and Y^1 together are substituted imidazole. Examples of second bases include sodium hydride, potassium hydride, lithium diisopropylamide and sodium bis(trimethylsilyl)amide.

SCHEME 3



[0178] Compounds having formula (3), may be converted to compounds having formula (4) by reacting the former, hydrogen and a hydrogenation catalyst. Examples of hydrogenation catalysts include Pd on carbon, platinum on carbon, and Raney nickel.

[0179] Compounds having formula (4) may be converted to compounds having formula (I), wherein B^1 and Y^1 together are triazole, by reacting the former, sodium nitrite, hydrochloric acid, and acetic acid. Compounds having formula (I), wherein B^1 and Y^1 together are triazole, may be reacted with the second base and the appropriate electrophile to provide compounds having formula (I), wherein B^1 and Y^1 together are substituted triazole.

[0180] The following examples are comparative: 32, 33, 53, 90-94, 98, 99, 128, 129, 133, 261-263, 265, 268, 271, 280, 308, 311, 322-332, 344, 431, 432, 437, 442 and 443. The remaining examples are encompassed within the scope of formula (I) of the appended claim 1.

EXAMPLE 1A

[0181] A mixture of piperazine (129.2 g), ethyl-4-fluorobenzoate (84 g), and K_2CO_3 (103.65 g) in DMSO (200 mL) at 120°C was stirred for 6 hours, poured into water, stirred for 30 minutes, and filtered.

EXAMPLE 1B

[0182] EXAMPLE 1A (200 mg) in dioxane at 40°C (4 mL) was treated with 2-(bromomethyl)-1,1'-biphenyl (232 mg) and DIEA (165 mg) and concentrated. The concentrate was flash chromatographed on silica gel with 20% ethyl acetate/hexanes.

EXAMPLE 1C

[0183] EXAMPLE 1B (340 mg) in 3:1:1 THF/methanol/water (4 mL) at 25°C was treated with LiOH·water (143 mg), stirred for 16 hours, and treated with 4M HCl (850 μL) and dichloromethane. The extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% methanol/dichloromethane.

EXAMPLE 1D

[0184] EXAMPLE 1C (112 mg) in dichloromethane (2.5 mL) at 25°C was treated with 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in commonly-owned International Application No. PCT/US01/29432, published as WO 02/24636, (115 mg), EDAC·HCl (109 mg), and DMAP (49 mg), stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 20% methanol/dichloromethane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.28 (d, 1H), 7.78 (dd, 1H), 7.72 (d, 2H), 7.54 (dd, 1H), 7.45-7.41 (m, 4H), 7.40-7.28 (m, 6H), 7.25 (td, 2H), 7.17 (tt, 1H), 6.88 (d, 1H), 6.78 (d, 2H), 4.10-4.01 (m, 1H), 3.41

(s, 2H), 3.33 (d, 2H), 3.14 (m, 4H), 2.82-2.62 (m, 2H), 2.44-2.35 (m, 10 H), 2.09-1.91 (m, 2H).

EXAMPLE 1E

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0185] EXAMPLE 1C (112 mg) in dichloromethane (2.5 mL) at 25°C was treated with EXAMPLE 1D (115 mg), EDAC·HCl (109 mg), and DMAP (49 mg), stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 20% methanol/dichloromethane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.28 (d, 1H), 7.78 (dd, 1H), 7.72 (d, 2H), 7.54 (dd, 1H), 7.45-7.41 (m, 4H), 7.40-7.28 (m, 6H), 7.25 (td, 2H), 7.17 (tt, 1H), 6.88 (d, 1H), 6.78 (d, 2H), 4.10-4.01 (m, 1H), 3.41 (s, 2H), 3.33 (d, 2H), 3.14 (m, 4H), 2.82-2.62 (m, 2H), 2.44-2.35 (m, 10H), 2.09-1.91 (m, 2H).

EXAMPLE 2A

[0186] A mixture of EXAMPLE 1A (23.43 g), 2-bromobenzyl bromide (26.24 g), and DIEA (20.94 mL) in acetonitrile (200 mL) at 25°C was stirred for 2 hours and filtered.

EXAMPLE 2B

[0187] A mixture of EXAMPLE 2A (13.83 g), 4-chlorophenyl-boronic acid (7.04 g), bis(triphenylphosphine)palladium dichloride (481 mg) and 2M sodium carbonate (22.5 mL) in 7:3:2 DME/water/ethanol (200 mL) at 90°C was stirred for 4.5 hours and extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5%-40% ethyl acetate/hexanes.

EXAMPLE 2C

[0188] A mixture of EXAMPLE 2B (13 g) and lithium hydroxide hydrate (3.78 g) in dioxane (250 mL) and water (100 mL) at 95°C was stirred for 16 hours and concentrated. The concentrate in water was heated at 80°C and filtered. The filtrate was treated with 1M HCl (90 mL) and filtered.

EXAMPLE 2D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0189] A mixture of EXAMPLE 2C (3.683 g), 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide (3.53 g), EDAC·HCl (3.32 g) and DMAP (2.12 g) in dichloromethane (500 mL) at 25°C was stirred for 8 hours, washed with saturated NH_4Cl (330 mL), and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 1%, 2%, 5%, 10%, and 15% methanol/NH_3-saturated dichloromethane. ^{1}H NMR (DMSO-d_6) δ 12.10 (br s, 1H), 11.18 (br s, 1H), 10.40 (br s, 1H), 8.54 (s, 1H), 8.29 (d, 1H), 8.10 (br s, 1H), 7.85 (d, 1H), 7.77 (d, 2H), 7.52 (d, 4H), 7.40-7.36 (m, 2H), 7.35-7.32 (m, 1H), 7.26-7.21 (m, 2H), 7.16-7.09 (m, 3H), 6.93 (d, 2H), 4.34 (br s, 2H), 4.35-4.23 (m, 1H), 3.88 (br s, 2H), 3.42-3.36 (m, 4H), 3.17-3.07 (m, 2H), 2.90-2.78 (m, 2H), 2.50 (s, 6H), 2.20-2.15 (m, 2H).

EXAMPLE 3A

[0190] This example was prepared by substituting 4-methoxyphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 3B

[0191] This example was prepared by substituting EXAMPLE 3A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 3C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0192] This example was prepared by substituting EXAMPLE 3B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.9 (br s, 1H), 9.57 (s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.72 (m, 1H), 7.50 (m, 2H), 7.33 (m, 1H), 7.29 (d, 2H), 7.23 (dd, 2H), 7.18 (d, 1H), 7.11 (m, 2H), 7.03 (d, 2H), 6.93 (d, 3H), 4.36 (br s, 2H), 4.18 (m, 1H), 3.80 (br s, 2H), 3.79 (s, 3H), 3.39 (d, 2H), 3.07 (m, 6H), 2.75 (s, 3H), 2.74 (s, 3H), 2.14 (q, 2H).

EXAMPLE 4A

[0193] This example was prepared by substituting 4-fluorophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 4B

[0194] This example was prepared by substituting EXAMPLE 4A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 4C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0195] This example was prepared by substituting EXAMPLE 4B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 10.00 (br s, 1H), 9.65 (s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (m, 2H), 7.41 (m, 2H), 7.34 (m, 1H), 7.29 (t, 2H), 7.23 (dd, 2H), 7.18 (d, 1H), 7.12 (m, 3H), 6.93 (d, 2H), 4.29 (br s, 4H), 4.19 (m, 1H), 3.84 (br s, 2H), 3.39 (d, 2H), 3.13 (m, 4H), 2.92 (m, 2H), 2.74 (s, 6H), 2.15 (m, 2H).

EXAMPLE 5A

[0196] This example was prepared by substituting 4-(methylsulfanyl)phenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 5B

[0197] This example was prepared by substituting EXAMPLE 5A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 5C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0198] This example was prepared by substituting EXAMPLE 5B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 9.9 (br s, 1H), 9.54 (s, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 7.85 (dd, 1H), 7.76 (d, 2H), 7.72 (m, 1H), 7.51 (dd, 2H), 7.33 (d, 2H), 7.31 (m, 1H), 7.29 (d, 2H), 7.21 (d, 2H), 7.16 (d, 1H), 7.10 (m, 3H), 6.92 (d, 2H), 4.32 (br s, 2H), 4.17 (m, 1H), 3.85 (br s, 4H), 3.38 (d, 2H), 3.11 (m, 5H), 2.90 (br s, 1H), 2.73 (s, 6H), 2.49 (s, 3H), 2.14 (m, 2H).

EXAMPLE 6A

[0199] This example was prepared by substituting 1,1'-biphenyl-4-ylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 6B

[0200] This example was prepared by substituting EXAMPLE 6A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 6C

N-((4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)-4-(4-(4'-phenyl-1,1'-biphenyl-2-ylmethyl)piperazin-1-yl)benzamide

[0201] This example was prepared by substituting EXAMPLE 6B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.9 (br s, 1H), 9.56 (s, 1H), 8.54. (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.75 (m, 7H), 7.56 (m, 2H), 7.48 (m, 4H), 7.39 (m, 2H), 7.22 (dd, 2H), 7.17 (d, 1H), 7.11 (m, 3H), 6.93 (d, 2H), 4.42 (br s, 2H), 4.18 (m, 1H), 3.83 (br s, 2H), 3.39 (d, 2H), 3.25 (br s, 2H), 3.13 (m, 4H), 2.91 (m, 2H), 2.74 (s, 6H), 2.14 (m, 2H).

EXAMPLE 7A

[0202] This example was prepared by substituting 4-phenoxyphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 7B

[0203] This example was prepared by substituting EXAMPLE 7A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 7C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0204] This example was prepared by substituting EXAMPLE 7B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 10.10 (br s, 1H), 9.64 (s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.73 (m, 1H), 7.51 (m, 2H), 7.38 (m, 5H), 7.23 (m, 2H), 7.14 (m, 5H), 7.07 (d, 4H), 6.95 (d, 2H), 4.33 (br s, 2H), 4.20 (m, 1H), 3.86 (br s, 2H), 3.39 (d, 2H), 3.25 (br s, 2H), 3.12 (m, 4H), 2.92 (m, 2H), 2.74 (s, 6H), 2.15 (m, 2H).

EXAMPLE 8

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0205] This example was prepared by substituting 4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.8 (br s, 1H), 8.53 (s, 1H), 8.51 (d, 1H), 7.83 (dd, 1H), 7.79 (d, 2H), 7.72 (br s, 1H), 7.52 (br s, 2H), 7.47 (t, 2H), 7.41 (t, 1H), 7.36 (d, 2H), 7.35 (m, 2H), 7.26 (d, 2H), 7.01 (t, 2H), 6.93 (d, 2H), 6.92 (d, 1H), 4.32 (br s, 2H), 3.79 (br s, 2H), 3.49 (br s, 4H), 3,14 (br s, 2H), 2.80 (br s, 2H), 1.56 (s, 6H).

EXAMPLE 9

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0206] This example was prepared by substituting 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (d, 1H), 8.40 (d, 1H), 7.89 (dd, 1H), 7.79 (d, 2H), 7.64 (m, 7H), 7.62 (d, 1H), 7.31 (d, 2H), 7.30 (d, 1H), 7.24 (dd, 2H), 7.19 (dd, 2H), 6.94 (d, 2H), 4.24 (m, 1H), 3.71 (m, 4H), 3.55 (m, 2H), 3.41 (d, 2H), 3.31 (m, 4H), 2.80 (m, 4H), 2.48 (m, 4H), 2.16 (m, 1H), 2.06 (m, 1H).

EXAMPLE 10

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0207] This example was prepared by substituting 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide), prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 8.74 (t, 1H), 8.58 (d, 1H), 7.89 (dd, 1H), 7.72 (d, 2H), 7.55 (m, 1H), 7.38 (m, 7H), 7.26 (m, 4H), 7.17 (m, 2H), 6.89 (d, 3H), 3.66 (m, 2H), 3.47 (m, 2H), 3.26 (m, 6H), 2.41 (m, 4H).

EXAMPLE 11

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0208] This example was prepared by substituting 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.93 (s, 1H), 8.66 (t, 1H), 8.56 (d, 1H), 7.89 (dd, 1H), 7.73 (d, 2H), 7.51 (d, 1H), 7.47 (m, 4H), 7.37 (m, 4H), 7.28 (t, 2H), 7.24 (m, 1H), 7.18 (t, 1H), 7.11 (d, 1H), 6.86 (d, 2H), 3.64 (q, 2H), 3.40 (s, 2H), 3.27 (q, 2H), 3.21 (m, 4H), 2.40 (m, 4H).

EXAMPLE 12

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0209] This example was prepared by substituting 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.98 (s, 2H), 8.55 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.72 (br s, 1H), 7.52 (d, 4H), 7.40 (d, 2H), 7.34 (m, 1H), 7.23 (d, 2H), 7.18 (d, 1H), 7.15 (t, 2H), 7.10 (m, 1H), 6.93 (d, 2H), 4.25 (br s, 2H), 4.19 (m, 1H), 3.95 (br s, 5H), 3.63 (br s, 4H), 3.40 (m, 4H), 3.18 (m, 4H), 3.02 (br s, 3H), 2.18 (m, 2H).

EXAMPLE 13

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0210] This example was prepared by substituting 4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzene-sulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 9.69 (br s, 1H), 8.53 (s, 1H), 8.51 (d, 1H), 7.83 (dd, 1H), 7.80 (d, 2H), 7.71 (br s, 1H), 7.52 (d, 4H), 7.40 (d, 2H), 7.37 (d, 1H), 7.33 (m, 1H), 7.26 (d, 2H), 7.01 (t, 2H), 6.93 (m, 3H), 4.33 (br s, 2H), 3.73 (br s, 4H), 3.12 (br s, 4H), 2.85 (br s, 2H), 1.56 (s, 6H).

EXAMPLE 14

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(dimethylamino)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[0211] This example was prepared by substituting 4-(((1R)-4-(dimethylamino)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzene-sulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.75 (br s, 1H), 9.26 (s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.34 (m, 1H), 7.23 (m, 3H), 7.11 (m, 3H), 6.93 (d, 2H), 4.30 (br s, 2H), 4.14 (m, 1H), 3.73 (br s, 6H), 3.37 (m, 2H), 3.02 (m, 4H), 2.72 (t, 6H), 1.77 (m, 4H).

EXAMPLE 15

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-5-(dimethylamino)-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide

[0212] This example was prepared by substituting 4-(((1R)-5-(dimethylamino)-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 1H), 10.96 (m, 1H), 9.99 (m, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 8.05 (m, 1H), 7.85 (dd, 1H), 7.75 (d, 2H), 7.53 (m, 4H), 7.36 (m, 4H), 7.23 (d, 2H), 7.11 (m, 3H), 6.93 (d, 2H), 4.35 (m, 1H), 4.12 (m, 1H), 3.92-3.87 (m, 2H), 3.53 (m, 8H), 3.27 (m, 2H), 2.94 (m 2H), 2.69 (s, 3H), 2.68 (s, 3H), 1.76 (m, 2H), 1.62 (m, 2H), 1.36 (m, 2H).

EXAMPLE 16

N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0213] This example was prepared by substituting 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, and EXAMPLE 4B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.93 (br s, 2H), 8.55 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.73 (br s, 1H), 7.52 (m, 2H), 7.41 (m, 2H), 7.34 (m, 1H), 7.29 (t, 2H), 7.23 (m, 2H), 7.18 (d, 1H), 7.12 (m, 3H), 6.93 (d, 2H), 4.28 (br s, 2H), 4.21 (m, 1H), 3.95 (br s, 5H), 3.63 (br s, 4H), 3.40 (m, 4H), 3.19 (m, 4H), 3.02 (br s, 3H), 2.18 (m, 2H).

EXAMPLE 17A

[0214] A mixture of EXAMPLE 1A (703 mg), 2-bromo-5-fluorobenzaldehyde (914 mg), 2.47 mmol/g MP-BH_3CN (4.05 g), and acetic acid (340 μL) in 1:1 methanol/dichloromethane (30 mL) was shaken for 1 day and filtered. The filtrate was concentrated, and the concentrate was flash chromatographed on silica gel with 5-50% ethyl acetate/hexanes.

EXAMPLE 17B

[0215] This example was prepared by substituting EXAMPLE 17A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 17C

[0216] This example was prepared by substituting EXAMPLE 17B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 17D

N-(4-(4-((4'-chloro-4-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0217] This example was prepared by substituting EXAMPLE 17C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.61 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.60 (bd, 1H), 7.52 (d, 2H), 7.37 (m, 4H), 7.23 (m, 2H), 7.18 (d, 1H), 7.12 (m, 3H), 6.94 (d, 2H), 4.18 (m, 3H), 3.80 (br s, 4H), 3.39 (d, 2H), 3.14 (m, 3H), 2.89 (s, 3H), 2.75 (s, 6H), 2.15 (m, 2H).

EXAMPLE 18A

[0218] 3-(R)-((carbobenzyloxy)amino)-γ-butyrolactone, prepared as described in J. Am. Chem. Soc. 1986, 108, 4943-4952, (7.72 g) in THF (100 mL) at 25°C was saturated with dimethylamine, stirred for 16 hours, and concentrated. The concentrate was filtered through a silica gel plug with 50% acetone/hexanes.

EXAMPLE 18B

[0219] EXAMPLE 18A (8.45 g) in toluene (15 mL) at 25°C was treated with tributylphosphine (9.76 mL) and diphe-

nyldisulfide (7.3 g), heated to 80°C for 16 hours and concentrated. The concentrate was flash chromatographed on silica gel with 0-50% ethyl acetate/hexanes.

EXAMPLE 18C

[0220] EXAMPLE 18B (10.60 g) in 30% HBr/acetic acid (50 mL) at 25°C was stirred for 18 hours, concentrated, treated with water (200 mL) and 5% HCl (100 mL), washed with diethyl ether, adjusted to pH 8-9 with Na_2CO_3, and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 18D

[0221] 1-fluoro-2-(trifluoromethyl)benzene (15 g) in chlorosulfonic acid (50 mL) and 1,2-dichloroethane (50 mL) at 70°C was stirred to for 2 hours, and concentrated. The concentrate in THF (200 mL) at to 0°C was treated with concentrated ammonium hydroxide (20 mL), stirred for 10 minutes, and poured into ethyl diethyl ether (500 mL). The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 30% ethyl acetate/hexanes.

EXAMPLE 18E

[0222] A mixture of EXAMPLE 18D (1.7 g) and EXAMPLE 18C (1.67 g) in DMSO (17 mL) was treated with DIEA (1.22 mL), heated at 110°C for 24 hours, poured into ethyl acetate (400 mL), washed with water and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 18F

[0223] EXAMPLE 18E (2.5 g) in THF (20 mL) at 25°C was treated with 1M borane·THF (22 mL), stirred for 24 hours, treated with methanol and concentrated. The concentrate in methanol (20 mL) was treated with HCl-saturated methanol (75 mL), stirred at reflux for 24 hours, concentrated, poured into 1M NaOH, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-5% TEA/ethyl acetate.

EXAMPLE 18G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0224] This example was prepared by substituting EXAMPLE 18F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^1H NMR (500 MHz, DMSO-d_6) δ 7.94 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 2H), 7.53 (dd, 1H), 7.47 (AB q, 4H), 7.41-7.33 (m, 5H), 7.36 (dd, 2H), 7.32 (d, 2H), 7.27 (m, 4H), 7.19 (dd, 1H), 6.89 (d, 2H), 6.87 (d, 1H), 5.94 (d, 1H), 3.94 (m, 1H), 3.42 (m, 2H), 3.26 (m, 4H), 3.10 (m, 1H), 2.96 (m, 1H), 2.67 (s, 6H), 2.41 (m, 4H), 2.13 (m, 2H).

EXAMPLE 19A

[0225] 3-(R)-((carbobenzyloxy)amino)-γ-butyrolactone, prepared as described in J. Am. Chem. Soc. 1986, 108, 4943-4952, (62 g) in dioxane (700 mL) was treated with morpholine (46 mL), heated to 65°C for 24 hours, cooled and concentrated. The concentrate was flash chromatographed on silica gel with 10% methanol in ethyl acetate.

EXAMPLE 19B

[0226] This example was prepared by substituting EXAMPLE 19A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 19C

[0227] This example was prepared by substituting EXAMPLE 19B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 19D

[0228] EXAMPLE 19C (45.4 g) in THF (500 mL) at 55°C was treated with 1M borane·THF in THF (650 mL), stirred for 24 hours, cooled to 0°C, treated with methanol, poured into methanol, and concentrated. The concentrate in methanol (400 mL) was treated with saturated HCl in methanol (800 mL), refluxed for 24 hours, concentrated, poured into 2M NaOH, and extracted with ethyl acetate. The extract was washed with 1M NaOH and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with ethyl acetate, 10% methanol/ethyl acetate, and 10% methanol/10% acetonitrile/5% TEA/75% ethyl acetate.

EXAMPLE 19E

[0229] This example was prepared by substituting EXAMPLE 19D for EXAMPLE 18C in EXAMPLE 18E.

EXAMPLE 19F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-9-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0230] This example was prepared by substituting EXAMPLE 19E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, 1H), 7.76 (dd, 1H), 7.72 (d, 2H), 7.50 (dd, 1H), 7.47 (s, 4H), 7.41-7.33 (m, 5H), 7.30 (d, 2H), 7.24 (dd, 1H), 7.19 (dd, 1H), 6.88 (d, 2H), 6.79 (d, 1H), 5.98 (d, 1H), 3.94 (m, 1H), 3.51 (m, 4H), 3.31-3.23 (m, 8H), 2.43 (m, 2H), 2.39 (m, 4H), 2.28 (m, 2H), 1.96 (m, 1H), 1.83 (m, 1H).

EXAMPLE 20A

[0231] 3-(R)-((carbobenzyloxy)amino)-γ-butyrolactone, prepared as described in J. Am. Chem. Soc. 1986, 108, 4943-4952, (1.8 g) in THF (20 mL) at 25°C was treated with pyrrolidine (3 mL), stirred for 3 days, and concentrated with a toluene azeotrope.

EXAMPLE 20B

[0232] This example was prepared by substituting EXAMPLE 20A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 20C

[0233] This example was prepared by substituting EXAMPLE 20B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 20D

[0234] EXAMPLE 20C (1.8 g) in DMF (30 mL) at 25°C was treated with TEA (950 μL) and 4-fluoro-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, (1.5 g), heated at 60°C for 150 minutes, poured into water, and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes. EXAMPLE 20E

[0235] EXAMPLE 20D (2.35 g) in THF (30 mL) at 25°C was treated with 1M borane·THF in THF (20 mL), stirred for 24 hours, cooled to 0°C, treated with methanol, poured into 6M HCl, stirred for 24 hours, cooled to 0°C, brought to pH 12 with KOH, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with ethyl acetate, 10% methanol/ethyl acetate, and 10% methanol/5% TEA/85% ethyl acetate.

EXAMPLE 20F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propyl)amino)benzenesulfonamide

[0236] This example was prepared by substituting EXAMPLE 20E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 9.73 (br s, 2H), 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (m, 4H), 7.39 (d, 2H), 7.34

(m, 1H), 7.23 (m, 2H), 7.18 (d, 1H), 7.12 (m, 3H), 6.92 (d, 2H), 4.22 (m, 3H), 3.86 (s, 4H), 3.51 (m, 2H), 3.38 (m, 2H), 3.21 (m, 4H), 2.94 (m, 4H), 2.15 (m, 2H), 2.00 (m, 2H), 1.84 (m, 2H).

EXAMPLE 21

[0237] 2-Amino-2-methyl-1-propanol (5 g) in dichloromethane (200 mL) at 0°C was treated with di-tert-butyldicarbonate (3.5 g) stirred for 8 hours at 25°C, washed with water, 5% aqueous citric acid, saturated $NaHCO_3$, and brine, and dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 21B

[0238] A mixture of EXAMPLE 21A (980 mg), 2-mercaptothiazole (610 mg), and triphenylphosphine (1.5 g) in THF (12 mL) at 25°C was stirred for 20 minutes, cooled to 0°C, treated with diisopropylazodicarboxylate (1.1 mL) in THF (6 mL), stirred at 25°C for 3 days, treated with ethyl acetate, washed with water and brine, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2%-10% ethyl acetate/hexanes.

EXAMPLE 21C

[0239] EXAMPLE 21B (410 mg) in diethyl ether (5 mL) at 25°C was treated with 4M HCl in 1,4-dioxane (5 mL), stirred for 2.5 hours, and filtered.

EXAMPLE 21D

[0240] A mixture of EXAMPLE 21C (300 mg) and 4-fluoro-3-nitrobenzenesulfonamide (300 mg), and DIEA (690 μL) in DMSO (2 mL) at 25°C was stirred for 18 hours, cooled to 15°C, treated with water (25 mL), acidified with 1M HCl, cooled to 0°C, stirred for 1 hour, and filtered.

EXAMPLE 21E

N-(4-(4-((4'-chloro(1,1'-biphenyl)- 2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0241] This example was prepared by substituting EXAMPLE 21D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^1H NMR (500MHz, DMSO-d_6) δ 8.59 (d, 1H), 8.49, (s, 1H), 7.90 (dd, 1H), 7.80 (d, 2H), 7.77 (s, 1H), 7.52 (d, 3H), 7.48 (d, 2H), 7.45 (dd, 2H), 7.40 (d, 2H), 7.40 (d, 1H), 6.93 (d, 2H), 4.24 (s, 2H), 3.86, (s, 2H), 3.35 (m, 6H), 2.85 (s, 2H), 1.58 (s, 6H).

EXAMPLE 22A

[0242] A mixture of 2-mercaptothiazole (4.6 g) and tetra-n-butylammonium persulfate, prepared as described in Tetrahedron Lett. 1993, 34, 3581-3584, (14.7g) in water (460 mL) at 25°C was stirred for 18 hours and extracted with diethyl ether. The extract was washed with brine and dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 22B

[0243] A mixture of EXAMPLE 18A (720 mg) and EXAMPLE 22A (770 mg) in toluene (9.1 mL) at 85°C was treated with tributylphosphine (830 μL), heated to 85°C, stirred for 5.5 hours, treated with ethyl acetate, washed with water and brine, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 30%-66% ethyl acetate/hexanes.

EXAMPLE 22C

[0244] This example was prepared by substituting EXAMPLE 22B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 22D

[0245] This example was prepared by substituting EXAMPLE 22C for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 22E

[0246] This example was prepared by substituting EXAMPLE 22D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 22F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0247] This example was prepared by substituting EXAMPLE 22E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.22 (d, 1H), 7.90 (dd, 1H), 7.72 (dd, 2H), 7.61 (d, 1H), 7.51 (m, 2H), 7.47 (s, 3H), 7.37 (m, 2H), 7.23, (m, 2H), 6.79 (d, 2H), 4.28 (m, 1H), 3.60 (m, 2H), 3.39 (s, 2H), 3.14 (m, 4H), 3.00 (m, 2H), 2.62 (s, 6H), 2.40 (m, 4H), 2.10 (m, 2H).

EXAMPLE 23A

[0248] This example was prepared by substituting 2-thienyldisulfide and THF for EXAMPLE 22A and toluene, respectively, in EXAMPLE 22B.

EXAMPLE 23B

[0249] This example was prepared by substituting EXAMPLE 23A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 23C

[0250] This example was prepared by substituting EXAMPLE 23B for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 23D

[0251] This example was prepared by substituting EXAMPLE 23C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 23E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0252] This example was prepared by substituting EXAMPLE 23D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.22 (d, 1H), 7.90 (dd, 1H), 7.82, (dd, 1H), 7.72 (d, 2H), 7.62 (dd, 1H), 7.51 (m, 1H), 7.47 (s, 3H), 7.37 (m, 2H), 7.25 (dd, 1H), 7.14 (dd, 1H), 7.02 (dd, 1H), 6.80 (m, 3H), 3.99 (m, 1H), 3.31 (m, 2H), 3.18 (m, 6H), 2.95 (m, 3H), 2.59 (s, 6H), 2.40 (t, 3H), 2.11 (m, 1H), 2.02 (m, 1H).

EXAMPLE 24A

[0253] N-tert-butoxycarbonyl-L-serine methyl ester (30 g) in dichloromethane (300 mL) at 0°C was treated with DIEA (59.7 mL) and methanesulfonylchloride (11.65 mL), stirred for 20 minutes, treated with thiophenol (15.5 mL), stirred at 25°C for 24 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 10-30% ethyl acetate/hexanes.

EXAMPLE 24B

[0254] EXAMPLE 24A (8.35 g) in dichloromethane (75 mL) was treated with 1M DIBAL in dichloromethane (94 mL) stirred for 2 hours, treated with methanol, poured into saturated NaH_2PO_4 (300 mL), stirred for 30 minutes, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 24C

[0255] 60% Oily NaH (480 mg) in dioxane (30 mL) at 25°C was treated with EXAMPLE 24B (1.7 g) in dioxane (10 mL), stirred for 10 minutes, treated with N,N-dimethylchloroacetamide (1.23 mL), heated at 70°C for 24 hours, poured into water, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 24D

[0256] EXAMPLE 24C (1.65 g) in THF (10 mL) at 25°C was treated with 1M borane·THF (20 mL), stirred for 24 hours, treated with 5M HCl (300 mL) and THF (300 mL), stirred for 2 days, cooled to 0°C, adjusted to pH 12 with KOH and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate in DME (30 mL) was treated with 4-fluoro-3-nitrobenzenesulfonamide (1 g) and TEA (627 μL), heated at 55°C for 90 minutes, poured into water, and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with ethyl acetate, 10% methanol/ethyl acetate, and 10% methanol/10% acetonitrile/80% ethyl acetate.

EXAMPLE 24E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0257] This example was prepared by substituting EXAMPLE 24D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (s, 1H), 10.90 (m, 1H), 9.90 (m, 1H), 8.56 (d, 1H), 8.52 (d, 1H), 8.04 (m, 1H), 7.86 (dd, 1H), 7.76 (d, 2H), 7.53 (m, 4H), 7.13-7.39 (m, 9H), 6.93 (d, 2H), 4.35 (m, 1H), 3.87-3.79 (m, 2H), 3.74 (m, 4H), 3.47 (m, 8H), 3.23 (m, 4H), 2.75 (m, 6H).

EXAMPLE 25A

[0258] Diethylamine (4.15 mL) in THF (150 mL) at -78 °C was treated with 2.5M n-butyllithium in hexanes (15.4 mL), stirred for 5 minutes at 0°C, cooled to -78°C, treated with (2R,4S)-3-((benzyloxy)carbonyl)-4-methyl-2-phenyl-1,3-oxazolidin-5-one, prepared as described in Helv. Chim. Acta 1991, 74, 800, (10 g) in THF (40 mL), stirred for 20 minutes, treated with allyl bromide (4.29 mL), stirred for 1 hour, stirred at 25°C for 18 hours, poured into pH 7 buffer, and extracted with diethyl ether. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% ethyl acetate/hexanes.

EXAMPLE 25B

[0259] EXAMPLE 25A (8.18 g) in methanol (200 mL) and water (20 mL) at 25°C was treated with LiOH·water (1.95 g), stirred for 30 minutes, poured into saturated NaH_2PO_4 (200 mL), and extracted with ethyl acetate. The extract was washed with 1M NaOH and brine and dried (Na_2SO_4), filtered, and concentrated. The base wash was acidified with 12M HCl and extracted with ethyl acetate. The extract was concentrated, and the concentrate in 1:1 ethyl acetate/methanol (50 mL) at 25°C was treated with 2M (trimethylsilyl)diazomethane in THF (5 mL), stirred for 10 minutes, and concentrated. The concentrates were combined and flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 25C

[0260] EXAMPLE 25B (5.03 g) in THF (75 mL) at 25°C was treated with 1M $LiBH(CH_2CH_3)_3$ in THF (38 mL), stirred for 2 hours, treated with methanol (30 mL), poured into water, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 30% ethyl acetate/hexanes.

EXAMPLE 25D

[0261] This example was prepared by substituting EXAMPLE 25C for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 25E

[0262] EXAMPLE 25D (2.9 g) in diethyl ether (45 mL) and tert-butanol (45 mL) at 25°C was treated with AD-mix-β (12.74 g), stirred for 18 hours, poured into saturated Na_2CO_3, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20-50%-ethyl acetate/hexanes. The product in THF (30 mL) and water (30 mL) at 25°C was treated with $NaIO_4$ (2.75 g), stirred for 20 minutes, poured into water, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 25F

[0263] EXAMPLE 25E (1.92 g) in dichloromethane (30 mL) at 25°C was treated with dimethylamine hydrochloride (684 mg), sodium triacetoxyborohydride (1.9 g), and TEA (1.56 mL), stirred for 24 hours, treated with methanol and water, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 25G

[0264] This example was prepared by substituting EXAMPLE 25F for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 25H

[0265] A mixture of EXAMPLE 25G (600 mg) and 4-fluoro-3-nitrobenzene-sulfonamide (554 mg) in DMSO (7 mL) at 25°C was treated with TEA (351 μL), heated at 60°C for 90 minutes, poured into water (30 mL), and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-10% methanol/ethyl acetate.

EXAMPLE 25I.

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0266] This example was prepared by substituting EXAMPLE 25H for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.14 (s, 1H), 10.90 (m, 1H), 10.22 (m, 1H), 8.50 (d, 1H), 8.32 (s, 1H), 8.04 (m, 1H), 7.83 (m, 3H), 7.54 (m, 4H), 7.36 (m, 4H), 7.23 (d, 2H), 6.98-6.85 (m, 5H), 4.35 (m, 2H), 3.92-3.87 (m, 2H), 3.74 (m, 2H), 3.48 (m, 8H), 3.23 (m, 2H), 2.70 (m, 6H), 1.56 (s, 3H).

EXAMPLE 26A

[0267] This example was prepared by substituting methylamine for dimethylamine in EXAMPLE 18A.

EXAMPLE 26B

[0268] This example was prepared by substituting EXAMPLE 26A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 26C

[0269] This example was prepared by substituting EXAMPLE 26B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 26D

[0270] This example was prepared by substituting EXAMPLE 26C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 26E

[0271] This example was prepared by substituting EXAMPLE 26D for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 26F

[0272] EXAMPLE 26E (1.12 g) in THF (7 mL) and acetonitrile (7 mL) at 25°C was treated with di-tert-butyldicarbonate (572 mg) and TEA (276 mg), stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 26G

[0273] This example was prepared by substituting EXAMPLE 26F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 26H

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0274] EXAMPLE 26G was flash chromatographed on silica gel with dichloromethane, 1:1 dichloromethane/ethyl acetate, and 10% (7M NH_3 in methanol) in methanol. A mixture of the free base in dichloromethane at 25°C was treated with 1:1 2M HCl/diethyl ether (10 mL), stirred for 18 hours and concentrated. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 1H), 10.94 (m, 1H), 8.71 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.05 (m, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.53 (m, 4H), 7.37 (m, 4H), 7.23 (m, 2H), 7.11 (m, 3H), 6.93 (d, 2H), 4.34 (m, 1H), 4.28 (m, 1H), 4.12 (m, 1H), 3.92-3.87 (m, 2H), 3.39 (m, 8H), 3.27 (m, 3H), 2.94 (m, 3H), 2.11 (m, 2H).

EXAMPLE 27A

[0275] A mixture of Fmoc-D-Asp(O-tert-butyl)-OH (10.25 g) and NMM (2.8 mL) in DME (30 mL) at -15°C was treated with isobutyl chloroformate (4.1 mL), stirred for 10 minutes, and filtered. The filtrate was cooled to 0°C, treated with $NaBH_4$ (2.84 g) in water (15 mL), stirred for 5 minutes, treated with water, stirred at 25°C for 3 hours, and filtered.

EXAMPLE 27B

[0276] A mixture of EXAMPLE 27A (9.5 g), diphenyl disulfide (7.86 g) and tributylphosphine (7.28 g) in toluene (200 mL) at 80°C was stirred for 5 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5% to 20% ethyl acetate/hexanes.

EXAMPLE 27C

[0277] This example was prepared by substituting EXAMPLE 27B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 27D

[0278] This example was prepared by substituting EXAMPLE 27C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 27E

(3R)-3-(9-(((4-(9-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanoic acid

[0279] EXAMPLE 27D (1 g) in dichloromethane (5 mL) at 25°C was treated with TFA (5 mL), stirred for 3 hours, and concentrated. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (d, 1H), 8.52 (d, 1H), 7.84 (dd, 1H), 7.75 (d, 2H), 7.55-7.35 (m, 7H), 7.27-7.11 (m, 6H), 6.91 (d, 2H), 4.39 (m, 1H), 3.39 (2, 2H), 3.31 (s, 8H), 3.26 (m, 2H), 2.81 (d, 2H).

EXAMPLE 28

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-4-(phenylsulfanyl)butanamide

[0280] A mixture of EXAMPLE 27E (160 mg) and N-methyl-morpholine (27 μL) in DMF (1 mL) at 25°C was treated with HATU (92 mg) and isopropylamine (50 μL), stirred for 5 hours, treated with ethyl acetate (200 mL), washed with 1% HCl, saturated $NaHCO_3$, water, and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane, (1:1) dichloromethane/ethyl acetate, and 5% methanol/dichloromethane. ^1H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, 1H), 8.52 (d, 1H), 7.93 (d, 1H), 7.83 (dd, 1H), 7.76 (d, 2H), 7.52 (m, 2H), 7.38 (m, 3H), 7.23 (m, 2H), 7.18-7.10 (m, 6H), 6.92 (d, 2H), 4.39 (m, 1H), 3.75 (m, 1H), 3.40 (m, 10H), 3.34 (m, 2H), 2.54 (m, 2H), 0.98 (d, 3H), 0.91 (d, 3H).

EXAMPLE 29A

[0281] EXAMPLE 27B (500 mg) in dichloromethane (3 mL) at 25°C was treated with TFA (3 mL), stirred for 3 hours, and concentrated with a dichloromethane azeotrope.

EXAMPLE 29B

[0282] A mixture of EXAMPLE 29A (450 mg) and NMM (140 μL) in DMF (3 mL) at 25°C was treated with HATU (464 mg) and diisopropylamine (283 μL), stirred for 5 hours, treated with ethyl acetate, washed with 1% HCl, saturated $NaHCO_3$, water, and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane, 1:1 dichloromethane/ethyl acetate, 5% methanol/dichloromethane.

EXAMPLE 29C

[0283] EXAMPLE 29B (200 mg) in THF (5 mL) at 25°C was treated with 2M borane·THF in THF (1 mL), stirred for 4 hours, treated with methanol (3 mL) and concentrated HCl (1 mL), stirred for 2 hours, brought to pH 7 with saturated $NaHCO_3$, and extracted with dichloromethane. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane and 5% methanol/dichloromethane.

EXAMPLE 29D

[0284] This example was prepared by substituting EXAMPLE 29C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 29E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0285] This example was prepared by substituting EXAMPLE 29D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^1H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.33 (s, 1H), 10.13 (s, 1H), 9.57 (s, 1H), 8.30 (d, 1H), 8.08 (d, 1H), 7.94 (m, 1H), 7.63 (dd, 1H), 7.55 (d, 2H), 7.30 (m, 4H), 7.15 (m, 2H), 7.09 (m, 1H), 6.99 (m, 3H), 6.89 (m, 3H), 6.71 (d, 2H), 4.11 (m, 1H), 3.61 (m, 8H), 3.19 (m, 1H), 3.17 (m, 2H), 2.94 (m, 1H), 2.77 (m, 4H), 2.62 (m, 1H), 2.05 (m, 1H), 1.53 (m, 2H), 1.09-0.75 (m, 12H).

EXAMPLE 30A

[0286] EXAMPLE 27C (2.2 g) in dichloromethane (25 mL) at 0°C was treated with TFA (25 mL) and water (2.5 mL), stirred at 25°C for 2 hours, and concentrated with a toluene azeotrope.

EXAMPLE 30B

[0287] EXAMPLE 30A (1 g) in DME (25 mL) at 25°C was treated with NMM (280 μL), cooled to -10°C, treated with isobutyl chloroformate (330 μL), stirred for 15 minutes, treated with sodium borohydride (277 mg) in water (10 mL), stirred for 45 minutes, and concentrated. The concentrate was treated with 0.5M HCl and extracted with ethyl acetate.

The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2% methanol/ dichloromethane and 4% methanol/dichloromethane.

EXAMPLE 30C

[0288] A mixture of EXAMPLE 30B (705 mg) and TEA (740 μL) in dichloromethane (8 mL) at 0°C was treated with SO_3·pyridine (850 mg) in DMSO (6 mL), stirred at 25°C for 30 minutes, treated 10% (w/v) aqueous citric acid, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 30D

[0289] EXAMPLE 30C (100 mg) and azetidine hydrochloride (20 mg) in acetonitrile (2 mL) at 25°C was treated with DIEA (44 μL) and sodium triacetoxyborohydride (67 mg), stirred for 16.5 hours, absorbed onto silica gel, concentrated, and flash chromatographed on silica gel with 5% methanol/dichloromethane and 10% methanol/NH_3-saturated dichloromethane.

EXAMPLE 30E

4-(((1R)-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0290] This example was prepared by substituting EXAMPLE 30D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.20 (d, 1H), 7.81 (dd, 1H), 7.71 (d, 2H), 7.35 (m, 14H), 6.88 (d, 1H), 6.78 (d, 2H), 4.05 (m, 1H), 3.79 (m, 4H), 3.33 (m, 5H), 3.13 (m, 5H), 2.40 (m, 4H), 2.24 (m, 2H), 1.89 (m, 2H).

EXAMPLE 31A

[0291] A mixture of 3,6-dioxa-bicyclo[3.1.0]hexane (3.44 g) and sodium azide (5.2 g) in water (10 mL) at 60°C was stirred for 24 hours and extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-40% ethyl acetate/hexanes.

EXAMPLE 31B

[0292] A mixture of EXAMPLE 31A (3.23 g), di-tert-butyl-dicarbonate (8.73 g), and 20 wt% palladium hydroxide on carbon (200 mg) in ethanol (15 mL) at 25°C was treated with triethylsilane (4.651 g), stirred at 50°C for 16 hours, filtered, and concentrated. The concentrate recrystallized from ethyl acetate/hexanes.

EXAMPLE 31C

[0293] A mixture of EXAMPLE 31B (2.03 g) and diphenyldisulfide (2.401 g) in toluene (20 mL) at 25°C was treated with tributylphosphine (2.224 g), stirred for 16 hours at 80°C, and concentrated. The concentrate was flash chromatographed on silica gel with 0%-40% ethyl acetate/hexanes.

EXAMPLE 31D

[0294] EXAMPLE 31C (590 mg) in 1:1 dioxane/dichloromethane (8 mL) at 25°C was treated with 4M HCl in dioxane (5 mL), stirred for 16 hours, and concentrated. The concentrate triturated with diethyl ether and filtered.

EXAMPLE 31E

[0295] This example was prepared by substituting EXAMPLE 31D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 31F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide

[0296] This example was prepared by substituting EXAMPLE 31E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (s, 1H), 9.70 (s, 1H), 8.69 (d, 1H), 8.54 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.74 (br s, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.34 (bd, 1H), 7.27 (m, 3H), 7.08 (t, 2H), 6.98 (t, 1H), 6.93 (d, 2H), 4.74 (quintet, 1H), 4.45 (q, 1H), 4.33 (dd, 1H), 4.17 (dd, 1H), 3.86 (br s, 2H), 3.77 (t, 1H), 3.75 (t, 1H), 3.49 (br s, 4H), 3.12 (br s, 2H), 2.89 (s, 2H).

EXAMPLE 32A

[0297] A mixture of magnesium turnings (432 mg) and one iodine crystal in diethyl ether (30 mL) at 25°C was treated with 2-bromobenzyl bromide (4.5 g), stirred for 3 hours, cooled to 0°C, treated with 4-(4-oxo-piperidine-1-yl)benzoic acid ethyl ester, prepared as described in Synthesis 1981, 606-608, (3.7 g) in 1:1 diethyl ether/THF (40 mL), stirred at 25°C for 18 hours, treated with aqueous NH_4Cl and extracted with ethyl acetate. The extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 32B

[0298] EXAMPLE 32A (1.6g) in THF (20 mL) at 25°C was treated with 60% oily sodium hydride (288 mg), heated at 50°C for 2 hours, treated with HMPA (3 mL) and methyl iodide (3.0 mL), stirred at reflux for 18 hours, cooled to 0°C, treated with aqueous $NaHSO_4$, and extracted with ethyl acetate. The extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10%-15% ethyl acetate/hexanes.

[0299] EXAMPLE 32C (and 25% (w/w) EXAMPLE 32B) A mixture of EXAMPLE 32B (640 mg), 4-chlorophenyl-boronic acid (465 mg), Pd(dppf)Cl_2 (122 mg), and cesium carbonate (1.46 g) in DMF (15 mL) at 80°C was stirred for 2 days and treated with ethyl acetate and brine. The water layer was extracted with ethyl acetate, and the extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5%-15% ethyl acetate/hexanes.

EXAMPLE 32D

[0300] This example was obtained by substituting EXAMPLE 32C for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 32E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0301] This example was prepared by substituting EXAMPLE 32D for EXAMPLE 2C in EXAMPLE 2D and purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.38 (s, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.69 (d, 2H), 7.46 (d, 2H), 7.28 (m, 7H), 7.15 (m, 4H), 6.82 (d, 2H), 4.18 (m, 1H), 3.40 (m, 4H), 3.13 (m, 2H), 3.04 (s, 3H), 2.86 (m, 4H), 2.74 (s, 6H), 2.14 (m, 2H), 1.47 (d, 2H), 1.18 (t, 2H).

EXAMPLE 33

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0302] This example was prepared by substituting 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, and EXAMPLE 32D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzene-sulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D and purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.69 (d, 2H), 7.46 (d, 2H), 7.30 (m, 7H), 7.14 (m, 4H), 6.82 (d, 2H), 4.18 (m, 1H), 3.95 (m, 2H), 3.67 (m, 4H), 3.39 (m, 4H), 3.19 (m, 2H), 3.03 (s, 3H), 3.00 (m, 2H), 2.85 (m, 4H), 2.17 (m, 2H), 1.47 (d, 2H), 1.17 (t, 2H).

EXAMPLE 34

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-hydroxy-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0303] EXAMPLE 27E (6.7 g) in DME (50 mL) at -15°C was treated with NMM (920 μL) and isobutyl chloroformate (1.09 mL), stirred for 20 minutes, treated with sodium borohydride (1.59 g) in water (10 mL), stirred for 30 minutes, treated with water, and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane, 1:1 dichloromethane/ethyl acetate, and 10% methanol/dichloromethane. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (d, 1H), 8.49 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.47 (m, 4H), 7.53-7.36 (m, 3H), 7.25 (m 2H), 7.19-7.07 (m, 4H), 6.91 (d, 2H), 4.69 (m, 1H), 4.21 (m, 1H), 3.49 (m, 2H), 3.35 (t, 2H), 3.31 (m, 8H), 3.27 (m, 2H), 1.89 (m, 2H).

EXAMPLE 35A

[0304] EXAMPLE 34 (786 mg) in dichloromethane (5 mL) at 25°C was treated with para-toluenesulfonic anhydride (326 mg), N,N-dimethylaminopyridine (122 mg), and DIEA (350 μL), stirred for 18 hours, treated with ethyl acetate, washed with 1% HCl, saturated $NaHCO_3$, and brine, and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 35B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0305] EXAMPLE 35A (100 mg) in DMF (2 mL) at 25°C was treated with DIEA (100 μL) and isopropylamine (60 μL), stirred at 50°C for 18 hours, treated with ethyl acetate, washed with saturated $NaHCO_3$, water, and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane, 1:1 dichloromethane/ethyl acetate, and 10% (7M NH_3 in methanol) in dichloromethane. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.09 (d, 1H), 7.84 (dd, 1H), 7.72 (d, 2H), 7.47 (m, 4H), 7.40-7.31 (m, 4H), 7.25 (m 3H), 7.17 (m, 2H), 6.94 (d, 1H), 6.78 (d, 2H), 4.11 (m, 1H), 3.37 (m, 2H), 3.30 (m, 8H), 3.12 (m, 2H), 2.99 (m, 2H), 2.40 (m, 2H), 2.05 (m, 2H), 1.16 (m, 6H).

EXAMPLE 36A

[0306] This example was made by substituting 2-napthaleneboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 36B

[0307] This example was made by substituting EXAMPLE 36A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 36C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(2-naphthyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0308] This example was made by substituting EXAMPLE 36B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 9.98 (br s, 1H), 9.60 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.81 (d, 2H), 7.49 (tt, 2H), 7.41 (m, 3H), 7.35 (m, 3H), 7.23 (m, 3H), 7.18 (d, 2H), 7.12 (m, 2H), 7.02 (d, 2H), 4.19 (m, 1H), 3.99 (br s, 2H), 3.39 (d, 4H), 3.29 (m, 4H), 3.14 (m, 2H), 2.98 (m, 2H), 2.75 (s, 6H), 2.14 (dd, 2H).

EXAMPLE 37A

[0309] This example was made by substituting 1-napthaleneboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 37B

[0310] This example was made by substituting EXAMPLE 37A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 37C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(1-naphthyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0311] This example was made by substituting EXAMPLE 37B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.59 (br s, 2H), 8.54 (d, 1H), 8.29 (d, 1H), 8.01 (dd, 2H), 7.85 (dd, 2H), 7.74 (d, 2H), 7.59 (m, 4H), 7.47 (m, 2H), 7.35 (d, 1H), 7.24 (m, 3H), 7.18 (d, 2H), 7.12 (m, 2H), 6.88 (d, 2H), 4.19 (m, 1H), 3.75 (br s, 2H), 3.39 (d, 4H), 3.29 (m, 4H), 3.14 (m, 2H), 2.98 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 38A

[0312] This example was made by substituting 3-cyanophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 38B

[0313] This example was made by substituting EXAMPLE 38A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 38C

N-(4-(4-((3'-cyano(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R) - 3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0314] This example was made by substituting EXAMPLE 38B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.47 (br s, 2H), 8.54 (d, 1H), 8.29 (d, 1H), 7.89 (d, 1H), 7.86 (dd, 2H), 7.77 (d, 2H), 7.69 (m, 3H), 7.56 (m, 2H), 7.37 (m, 1H), 7.24 (m, 2H), 7.14 (d, 5H), 6.93 (d, 2H), 4.18 (m, 1H), 4.04 (m, 2H), 3.75 (m, 2H), 3.39 (d, 4H), 3.15 (m, 4H), 3.06 (m, 2H), 2.75 (s, 3H), 2.74 (s, 3H), 2.14 (dd, 2H).

EXAMPLE 39A

[0315] This example was made by substituting 3-methoxyphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 39B

[0316] This example was made by substituting EXAMPLE 39A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 39C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((3'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0317] This example was made by substituting EXAMPLE 39B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.58 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.72 (m, 1H), 7.50 (m, 2H), 7.37 (m, 2H), 7.24 (m, 2H), 7.14 (d, 4H), 6.98 (m, 1H), 6.92 (m, 4H), 4.31 (br s, 2H), 4.18 (m, 1H), 3.79 (s, 3H), 3.39 (d, 3H), 3.15 (m, 5H), 2.75 (s, 6H), 2.14 (dd, 2H).

EXAMPLE 40A

[0318] This example was made by substituting 3-chlorophenyl-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 40B

[0319] This example was made by substituting EXAMPLE 40A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 40C

N-(4-(4-((3'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0320] This example was made by substituting EXAMPLE 40B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.86 (br s, 1H), 9.59 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.70 (m, 1H), 7.49 (m, 5H), 7.34 (m, 2H), 7.24 (m, 2H), 7.14 (d, 4H), 6.94 (d, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.13 (m, 5H), 2.88 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 41A

[0321] This example was made by substituting 2-chlorophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 41B

[0322] This example was made by substituting EXAMPLE 41A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 41C

N-(4-(4-((2'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0323] This example was made by substituting EXAMPLE 41B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 10.00 (br s, 1H), 9.59 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.76 (m, 1H), 7.58 (m, 3H), 7.45 (m, 3H), 7.28 (dd, 1H), 7.23 (m, 2H), 7.14 (d, 4H), 6.94 (d, 2H), 4.18 (m, 1H), 3.39 (d, 3H), 3.13 (m, 5H), 3.02 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 42A

[0324] This example was made by substituting 3,4-methylene-dioxybenzeboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 42B

[0325] This example was made by substituting EXAMPLE 42A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 42C

N-(4-(4-(2-(1,3-benzodioxol-5-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0326] This example was made by substituting EXAMPLE 42B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.85 (br s, 1H), 9.55 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.69 (m, 1H), 7.48 (br s, 2H), 7.31 (m, 1H), 7.23 (m, 2H), 7.14 (d, 4H), 6.96 (m, 4H), 6.79 (dd, 1H), 6.06 (s, 2H), 4.18 (m, 1H), 3.39 (d, 3H), 3.12 (m, 5H), 2.86 (m, 2H), 2.75 (s, 6H), 2.14 (dd, 2H).

EXAMPLE 43A

[0327] This example was made by substituting thiophene-3-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 43B

[0328] This example was made by substituting EXAMPLE 43A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 43C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(3-thienyl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0329] This example was made by substituting EXAMPLE 43B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.99 (br s, 1H), 9.62 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.69 (m, 2H), 7.63 (s, 1H), 7.48 (br s, 2H), 7.41 (m, 1H), 7.24 (m, 2H), 7.14 (d, 5H), 6.95 (d, 2H), 4.18 (m, 1H), 3.39 (d, 3H), 3.14 (m, 5H), 2.89 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 44A

[0330] This example was made by substituting pyridine-3-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 44B

[0331] This example was made by substituting EXAMPLE 44A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 44C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(pyridin-3-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0332] This example was made by substituting EXAMPLE 44B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.99 (br s, 1H), 9.66 (br s, 1H), 8.69 (dd, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.95 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.59 (m, 3H), 7.40 (m, 1H), 7.24 (m, 2H), 7.14 (d, 4H), 6.93 (d, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.14 (m, 5H), 2.92 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 45A

[0333] This example was made by substituting 8-quinolineboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 45B

[0334] This example was made by substituting EXAMPLE 45A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 45C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(quinolin-8-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0335] This example was made by substituting EXAMPLE 45B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.84 (br s, 1H), 9.61 (br s, 1H), 8.84 (dd, 1H), 8.54 (d, 1H), 8.48 (dd, 1H), 8.29 (d, 1H), 8.10 (td, 1H), 7.85 (dd, 1H), 7.80 (d, 1H), 7.73 (m, 4H), 7.56 (m, 3H), 7.35 (dd, 1H), 7.23 (m, 3H), 7.14 (m, 3H), 6.89 (d, 2H), 4.29 (m, 1H), 4.20 (m, 1H), 3.90 (d, 1H), 3.39 (d, 4H), 3.14 (m, 3H), 2.97 (m, 3H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 46A

[0336] This example was made by substituting benzofuran-2-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 46B

[0337] This example was made by substituting EXAMPLE 46A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 46C

N-(4-(4-(2-(1-benzofuran-2-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0338] This example was made by substituting EXAMPLE 46B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.14 (br s, 1H), 9.81 (br s, 1H), 9.63 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.97 (d, 1H), 7.86 (dd, 1H), 7.81 (d, 2H), 7.69 (m, 3H), 7.60 (m, 2H), 7.46 (s, 1H), 7.38 (td, 1H), 7.32 (t, 1H), 7.22 (m, 2H), 7.15 (d, 4H), 7.01 (d, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.27 (m, 2H), 3.15 (m, 5H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 47A

[0339] This example was made by substituting 2-methylphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 47B

[0340] This example was made by substituting EXAMPLE 44A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 47C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0341] This example was made by substituting EXAMPLE 44B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.94 (br s, 1H), 9.73 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.50 (m, 2H), 7.31 (d, 2H), 7.22 (m, 9H), 6.94 (d, 2H), 4.19 (m, 1H), 3.39 (d, 4H), 3.16 (m, 4H), 2.92 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 48A

[0342] This example was made by substituting 3-quinolineboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 48B

[0343] This example was made by substituting EXAMPLE 48A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 48C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(quinolin-3-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0344] This example was made by substituting EXAMPLE 48B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.93 (br s, 1H), 9.56 (br s, 1H), 8.53 (d, 1H), 8.42 (s, 1H), 8.28 (d, 1H), 8.09 (d, 1H), 8.04 (dd, 1H), 7.85 (dd, 1H), 7.82 (m, 2H), 7.74 (d, 2H), 7.68 (td, 1H), 7.50 (m, 2H), 7.23 (m, 2H), 7.14 (d, 4H), 6.90 (d, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.14 (m, 5H), 2.90 (m, 2H), 2.74 (s, 6H), 2.13 (dd, 2H).

EXAMPLE 49A

[0345] A mixture of EXAMPLE 1A (272 mg), 1-bromo-naphthalene-2-carbaldehyde (0.409 g), MP-BH_3CN (2.47 mmol/g, 1.41 g) and acetic acid (0.14 g) in 1:1 methanol/dichloromethane (8 mL) was shaken for 1 day at 25°C, filtered, and concentrated. The concentrate was treated with saturated aqueous K_2CO_3 and dichloromethane, and the organic layer was dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 5%-50% ethyl acetate/hexanes.

EXAMPLE 49B

[0346] This example was made by substituting EXAMPLE 49A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 49C

[0347] This example was made by substituting EXAMPLE 49B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 49D

N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0348] This example was made by substituting EXAMPLE 49C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)-methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.87 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 8.29 (d, 1H), 8.13 (d, 1H), 8.04 (d, 1H), 7.90 (dd, 1H), 7.86 (d, 1H), 7.77 (d, 2H), 7.62 (d, 2H), 7.60 (m, 1H), 7.50 (t, 1H), 7.37 (m, 3H), 7.28 (d, 2H), 7.19 (m, 2H), 6.94 (d, 2H), 4.23 (br s, 2H), 3.82 (br s, 4H), 3.67 (dd, 2H), 3.28 (m, 2H), 3.16 (br s, 2H), 2.97 (br s, 2H).

EXAMPLE 50

N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0349] This example was made by substituting EXAMPLE 49C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 9.97 (br s, 1H), 9.56 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 8.12 (d, 1H), 8.05 (d, 1H), 7.87 (d, 1H), 7.86 (d, 1H), 7.79 (d, 2H), 7.61 (m, 3H), 7.50 (m, 1H), 7.38 (d, 2H), 7.28 (d, 1H), 7.22 (m, 2H), 7.14 (m, 4H), 6.95 (d, 2H), 4.25 (br s, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.14 (m, 5H), 2.94 (m, 2H), 2.75 (s, 3H), 2.74 (s, 3H), 2.15 (dd, 2H).

EXAMPLE 51

N-(4-(4-((1-(4-chlorophenyl)-2-naphthyl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0350] This example was made by substituting EXAMPLE 49C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.89 (br s, 2H), 8.55 (d, 1H), 8.29 (d, 1H), 8.12 (d, 1H), 8.04 (d, 1H), 7.86 (m, 2H), 7.78 (d, 2H), 7.62 (d, 2H), 7.60 (m, 1H), 7.50 (t, 1H), 7.38 (d, 2H), 7.28 (d, 1H), 7.15 (d, 4H), 6.95 (d, 2H), 4.19 (m, 1H), 3.95 (m, 4H), 3.62 (m 3H), 3.41 (d, 5H), 3.18 (m, 5H), 3.01 (br s, 4H), 2.19 (dd, 2H).

EXAMPLE 52A

[0351] A mixture of 6-oxa-bicyclo[3.1.0]hexane (1.68 g) and NaN_3 (2.6 g) in water (5 mL) at 60°C was stirred for 3 days. The water layer was extracted with dichloromethane, and the extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel 0-40% ethyl acetate/hexanes.

EXAMPLE 52B

[0352] A mixture of EXAMPLE 52A (1.017 g), di(tert-butyl) dicarbonate (2.619 g), $Pd(OH)_2$ (100 mg) and triethylsilane (1.395 g) in ethanol (15 mL) at 50 °C was stirred for 16 hours, concentrated partially, and partitioned between ethyl acetate and water. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10-60% ethyl acetate/hexanes.

EXAMPLE 52C

[0353] A mixture of EXAMPLE 52B (0.201 g) and diphenyldisulfide (262 mg) in toluene (2 mL) at 25°C was teated with tri-n-butylphosphine (243 mg), stirred for 16 hours at 80°C, and concentrated. The concentrate was flash chromatographed on silica gel 0-30% ethyl acetate/hexanes.

EXAMPLE 52D

[0354] A mixture of EXAMPLE 52C (0.325 g) and 4M HCl in dioxane (2.5 mL) in dichloromethane (3 mL) at 25°C was stirred for 3 hours and partially concentrated. The concentrate was treated with diethyl ether and filtered.

EXAMPLE 52E

[0355] This example was prepared by substituting EXAMPLE 52D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 52F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)cyclopentyl)amino)benzenesulfonamide

[0356] This example was made by substituting EXAMPLE 52E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.77 (br s, 1H), 8.55 (d, 1H), 8.36 (d, 1H), 7.85 (dd, 1H), 7.77 (d, 2H), 7.73 (m, 1H), 7.54 (m, 4H), 7.39 (td, 2H), 7.33 (m, 3H), 7.17 (m, 4H), 6.93 (d, 2H), 4.32 (br s, 2H), 4.10 (br s, 2H), 4.09 (quintet, 1H), 3.85 (q, 1H), 3.39 (d, 3H), 3.25 (br s, 2H), 3.10 (br s, 2H), 2.89 (br s, 2H), 2.25 (sextet, 2H), 1.79 (m, 2H), 1.64 (m, 2H).

EXAMPLE 53

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)cyclopentyl)amino)benzenesulfonamide

[0357] This example was made by substituting EXAMPLE 52E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, in EXAMPLE 32E. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (br s, 1H), 8.55 (d, 1H), 8.35 (d, 1H), 7.85 (dd, 1H), 7.68 (d, 2H), 7.42 (t, 2H), 7.35 (m, 3H), 7.28 (m, 3H), 7.16 (m, 4H), 6.82 (d, 2H), 4.09 (quintet, 1H), 3.84 (q, 1H), 3.39 (d, 2H), 3.03 (s, 3H), 2.89 (s, 2H), 2.83 (t, 1H), 2.25 (sextet, 2H), 1.79 (m, 2H), 1.64 (m, 2H), 1.47 (d, 2H), 1.17 (m, 2H).

EXAMPLE 54

N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0358] This example was made by substituting 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 4C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 9.72 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 7.90 (dd, 1H), 7.75 (d, 2H), 7.71 (m, 1H), 7.52 (br s, 2H), 7.41 (dd, 2H), 7.35 (m, 2H), 7.28 (m, 2H), 7.19 (m, 2H), 6.92 (d, 2H), 4.24 (br s, 2H), 3.80 (br s, 2H), 3.66 (q, 2H), 3.28 (t, 2H), 3.14 (br s, 2H), 2.86 (br s, 2H).

EXAMPLE 55A

[0359] This example was made by substituting 3,4-dichlorophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 55B

[0360] This example was made by substituting EXAMPLE 55A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 55C

N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0361] This example was made by substituting EXAMPLE 55B and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenyl-

sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.71 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 7.90 (dd, 1H), 7.76 (d, 2H), 7.73 (m, 1H), 7.71 (d, 2H), 7.54 (m, 2H), 7.36 (m, 4H), 7.26 (tt, 2H), 7.18 (m, 2H), 6.94 (d, 2H), 4.28 (br s, 2H), 3.85 (br s, 2H), 3.67 (q, 2H), 3.28 (t, 2H), 3.12 (br s, 2H), 2.93 (br s, 2H).

EXAMPLE 56

N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0362] This example was made by substituting EXAMPLE 55B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.94 (br s, 1H), 9.64 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.74 (m, 1H), 7.71 (d, 1H), 7.69 (br s, 1H), 7.54 (m, 2H), 7.37 (m, 2H), 7.23 (m, 2H), 7.14 (m, 4H), 6.95 (d, 2H), 4.31 (br s, 2H), 4.20 (m, 1H), 3.93 (br s, 2H), 3.39 (d, 3H), 3.14 (m, 5H), 2.90 (m, 2H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 57

N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0363] This example was made by substituting EXAMPLE 55B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 10.32 (br s, 1H), 9.98 (br s, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.71 (br s, 1H), 7.70 (d, 2H), 7.53 (m, 2H), 7.36 (m, 2H), 7.24 (m, 2H), 7.15 (m, 4H), 6.94 (d, 2H), 4.25 (br s, 2H), 4.19 (m, 1H), 3.95 (m, 4H), 3.63 (m, 3H), 3.40 (d, 5H), 3.19 (m, 4H), 3.02 (br s, 4H), 2.18 (dd, 2H).

EXAMPLE 58A

[0364] This example was made by substituting 4-trifluoromethylphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 58B

[0365] This example was made by substituting EXAMPLE 58A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 58C

3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0366] This example was made by substituting EXAMPLE 58B and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.85 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 7.90 (dd, 1H), 7.83 (d, 2H), 7.78 (br s, 1H), 7.76 (d, 2H), 7.61 (d, 2H), 7.54 (m, 2H), 7.37 (m, 3H), 7.26 (t, 2H), 7.19 (t, 2H), 6.93 (d, 2H), 4.30 (br s, 2H), 4.00 (br s, 4H), 3.67 (q, 2H), 3.28 (t, 2H), 3.10 (br s, 2H), 2.94 (br s, 2H).

EXAMPLE 59

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0367] This example was made by substituting EXAMPLE 58B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 10.01 (br s, 1H), 9.60 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.82 (d, 2H), 7.78 (br s, 1H), 7.77 (d, 2H), 7.61 (d, 2H), 7.56 (m, 2H), 7.37 (m, 1H), 7.23 (m, 2H), 7.14 (m, 4H), 6.93 (d, 2H), 4.25 (br s, 2H), 4.19 (m, 1H), 3.98 (br s, 2H), 3.39 (d, 3H), 3.13 (m, 5H), 2.90 (m, 2H), 2.74 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 60

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0368] This example was made by substituting EXAMPLE 58B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.99 (br s, 2H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.83 (d, 2H), 7.79 (br s, 1H), 7.77 (d, 2H), 7.60 (d, 2H), 7.57 (m, 2H), 7.38 (m, 1H), 7.23 (m, 2H), 7.14 (m, 4H), 6.93 (d, 2H), 4.32 (br s, 2H), 4.19 (m, 1H), 3.95 (m, 2H), 3.62 (m, 3H), 3.40 (m, 5H), 3.20 (m, 4H), 3.02 (br s, 4H), 2.18 (dd, 2H).

EXAMPLE 61A

[0369] This example was made by substituting 4-trifluoromethoxyboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 61B

[0370] This example was made by substituting EXAMPLE 61A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 61C

3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0371] This example was made by substituting EXAMPLE 61B and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.78 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 7.90 (dd, 1H), 7.76 (d, 2H), 7.75 (br s, 1H), 7.54 (m, 2H), 7.50 (d, 2H), 7.45 (d, 2H), 7.37 (m, 3H), 7.26 (t, 2H), 7.18 (m, 2H), 6.93 (d, 2H), 4.30 (br s, 2H), 3.98 (br s, 4H), 3.67 (q, 2H), 3.28 (t, 2H), 3.11 (br s, 2H), 2.89 (br s, 2H).

EXAMPLE 62

3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(trifluoromethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0372] This example was made by substituting EXAMPLE 61B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 10.05 (br s, 1H), 9.62 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.76 (br s, 1H), 7.54 (m, 2H), 7.50 (d, 2H), 7.45 (d, 2H), 7.37 (m, 1H), 7.23 (m, 2H), 7.14 (m, 4H), 6.93 (d, 2H), 4.31 (br s, 2H), 4.19 (m, 1H), 3.82 (br s, 2H), 3.39 (d, 3H), 3.13 (m, 5H), 2.92 (m, 2H), 2.74 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 63

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-(trifluoromethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0373] This example was made by substituting EXAMPLE 61B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 9.99 (br s, 2H), 8.55 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.76 (br s, 1H), 7.54 (m, 2H), 7.51 (d, 2H), 7.45 (d, 2H), 7.37 (m, 1H), 7.23 (m, 2H), 7.14 (m, 4H), 6.93 (d, 2H), 4.30 (br s, 2H), 4.20 (m, 1H), 3.95 (m, 2H), 3.63 (m, 3H), 3.40 (m, 5H), 3.20 (m, 4H), 3.02 (br s, 4H), 2.18 (dd, 2H).

EXAMPLE 64A

[0374] This example was made by substituting 4-phenoxyphenylboronic acid for 4-chlorophenylboronic acid in EX-

AMPLE 2B.

EXAMPLE 64B

[0375] This example was made by substituting EXAMPLE 64A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 64C

3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0376] This example was made by substituting EXAMPLE 64B and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((lR)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 9.76 (br s, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 7.91 (dd, 1H), 7.77 (d, 2H), 7.73 (br s, 1H), 7.52 (m, 2H), 7.38 (m, 7H), 7.26 (t, 2H), 7.18 (m, 3H), 7.07 (m, 4H), 6.94 (d, 2H), 4.36 (br s, 2H), 3.80 (br s, 4H), 3.67 (q, 2H), 3.28 (t, 2H), 3.15 (br s, 2H), 2.87 (br s, 2H).

EXAMPLE 65

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0377] This example was made by substituting EXAMPLE 64B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.98 (br s, 2H), 8.56 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.73 (br s, 1H), 7.51 (m, 2H), 7.38 (m, 5H), 7.23 (m, 2H), 7.15 (m, 5H), 7.07 (d, 4H), 6.95 (d, 2H), 4.31 (br s, 2H), 4.20 (m, 1H), 3.94 (m, 2H), 3.63 (m, 3H), 3.40 (m, 5H), 3.19 (m, 4H), 3.02 (br s, 4H), 2.18 (dd, 2H).

EXAMPLE 66A

[0378] ADDP (11.43 g) in THF (100 mL) at 25°C was treated with tributylphosphine (9.16 g), stirred for 10 minutes, treated with (S)-3-tert-butoxycarbonylamino-4-hydroxybutyric acid cyclohexyl ester (9.1 g), prepared as described in Tet. Lett. (1995), 36(8), 1223, in THF (20 mL) and thiophenol (6.61 g), stirred for 2 days, treated with diethyl ether, and filtered. The filtrate was concentrated, and the concentrate was flash chromatographed on silica gel with 0-15% ethyl acetate/hexane.

EXAMPLE 66B

[0379] A mixture of EXAMPLE 66A (7.1 g) and 4M HCl in dioxane (30 mL) was stirred for 5 hours and concentrated.

EXAMPLE 66C

[0380] This example was made by substituting EXAMPLE 66B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 66D

[0381] A mixture of EXAMPLE 66C (8.341 g) and lithium hydroxide (1.426 g) in 1:1 THF/water (100 mL) was stirred for 18 hours at 25°C, partially concentrated, treated with water (250 mL), washed with dichloromethane/ethyl acetate, acidified with 12M HCl to pH 2, and extracted with ethyl acetate. The extract was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 66E

[0382] A mixture of EXAMPLE 66D (6.42 g) and NMM (1.67 g) in DME (70 mL) at 0-5 °C was treated with isobutyl chloroformate (2.14 mL), stirred for 5 minutes treated with 2M dimethylamine in THF (40 mL), stirred at 25°C, concentrated, and filtered.

EXAMPLE 66F

[0383] This example was made by substituting EXAMPLE 66E for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 66G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0384] This example was made by substituting EXAMPLE 66F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (br s, 1H), 8.47 (d, 1H), 8.19 (d, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.51 (m, 1H), 7.47 (s, 4H), 7.37 (m, 2H), 7.30 (m, 2H), 7.24 (t, 3H), 7.16 (m, 1H), 6.93 (d, 1H), 6.80 (d, 2H), 4.07 (br s, 2H), 3.39 (m, 2H), 3.33 (m, 2H), 3.14 (m, 4H), 3.00 (m, 2H), 2.63 (s, 6H),2.40 (m, 4H), 2.08 (m, 2H).

EXAMPLE 67A

[0385] ADDP (16.94 g) in THF (90 mL) at 25°C was treated with tributylphosphine (13.55 g), stirred for 10 minutes, treated with (2-hydroxy-1,1-dimethylethyl)carbamic acid tert-butyl ester (8.47 g), prepared as described in Synlett. (1997), (8), 893-894, in THF (30 mL) and thiophenol (7.38 g), stirred for 1 day, treated with diethyl ether, and filtered. The filtrate was concentrated, and the concentrate was flash chromatographed on silica gel 0-15% ethyl acetate/hexanes.

EXAMPLE 67B

[0386] A mixture of EXAMPLE 67A (0.562 g) and 80% magnesium monoperoxy pthalic acid (1.36 g) in THF (10 mL) was stirred for 18 hours, treated with dichloromethane, and filtered. The filtrate was washed with brine and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel 10-50% ethyl acetate/hexanes.

EXAMPLE 67C

[0387] This example was made by substituting EXAMPLE 67B for EXAMPLE 66A in EXAMPLE 66B.

EXAMPLE 67D

[0388] This example was made by substituting EXAMPLE 67C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 67 E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfonyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0389] This example was made by substituting EXAMPLE 67D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.69 (br s, 1H), 8.44 (d, 1H),8.33 (s, 1H), 7.82 (d, 2H), 7.71 (dd, 2H), 7.64 (td, 2H), 7.52 (d, 3H), 7.40 (d, 2H), 7.32 (m, 1H), 7.25 (d, 1H), 7.23 (tt, 1H), 7.16 (tt, 2H), 6.95 (d, 2H), 4.30 (br s, 2H), 4.13 (s, 2H), 3.84 (br s, 2H), 3.13 (br s, 4H), 2.86 (br s, 2H). 1. 62 (s, 6H).

EXAMPLE 68A

[0390] This example was made by substituting 2,4-dichlorophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 68B

[0391] This example was made by substituting EXAMPLE 68A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 68C

[0392] N-(4-(4-((2',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0393] This example was made by substituting EXAMPLE 68B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.89 (br s, 1H), 9.56 (br s, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.85 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (m, 3H), 7.43 (d, 1H), 7.26 (d, 1H), 7.22 (d, 2H), 7.13 (m, 4H), 6.94 (d, 2H), 4.26 (br s, 2H), 4.17 (m, 1H), 3.38 (d, 3H), 3.13 (m, 7H), 2.74 (s, 6H), 2.14 (dd, 2H).

EXAMPLE 69A

[0394] This example was made by substituting thiophene-2-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 69B

[0395] This example was made by substituting EXAMPLE 69A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 69C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(2-thienyl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0396] This example was made by substituting EXAMPLE 69B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.95 (br s, 1H), 9.55 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.73 (m, 1H), 7.68 (d, 1H), 7.51 (m, 3H), 7.24 (m, 2H), 7.17 (m, 2H), 7.14 (m, 4H), 6.96 (d, 2H), 4.41 (br s, 2H), 4.18 (m, 1H), 3.38 (d, 3H), 3.13 (m, 7H), 2.75 (s, 6H), 2.15 (dd, 2H).

EXAMPLE 70A

[0397] This example was made by substituting 4-chloro-2-methylphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 70B

[0398] This example was made by substituting EXAMPLE 70A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 70C

N-(4-(4-((4'-chloro-2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0399] This example was made by substituting EXAMPLE 70B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (m, 1H), 9.60 (s, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 7.85 (dd, 1H), 7.77 (d, 3H), 7.52 (m, 2H), 7.41 (d, 1H), 7.31 (dd, 1H), 7.20 (m, 4H), 7.12 (m, 4H), 6.94 (d, 1H), 4.18 (m, 1H), 3.85 (m, 7H), 3.38 (d, 2H), 3.11 (m, 6H), 2.74 (s, 6H), 2.14 (dd, 2H), 1.96 (s, 3H).

EXAMPLE 71A

[0400] This example was made by substituting 2,4-difluorophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 71B

[0401] This example was made by substituting EXAMPLE 71A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 71C

N-(4-(4-((2',4'-difluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0402] This example was made by substituting EXAMPLE 71B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 9.53 (br s, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 7.85 (dd, 1H), 7.76 (d, 2H), 7.54 (quintet, 2H), 7.44 (m, 1H), 7.35 (m, 2H), 7.15 (m, 6H), 6.93 (d, 2H), 4.17 (m, 1H), 3.38 (d, 2H), 3.12 (m, 4H), 2.74 (s, 3H), 2.73 (s, 3H), 2.13 (dd, 2H).

EXAMPLE 72A

[0403] This example was made by substituting (2-benzenesulfonylethyl)carbamic acid tert-butyl ester, prepared as described in WO2001-US11395, for EXAMPLE 66A in EXAMPLE 66B.

EXAMPLE 72B

[0404] This example was made by substituting EXAMPLE 72A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 72C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzenesulfonamide

[0405] This example was made by substituting EXAMPLE 72B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.60 (br s, 1H), 8.56 (d, 1H), 8.55 (m, 1H), 7.91 (dd, 1H), 7.84 (m, 2H), 7.75 (d, 3H), 7.67 (tt, 1H), 7.54 (m, 2H), 7.48 (m, 4H), 7.37 (m, 3H), 7.13 (d, 2H), 6.92 (d, 2H), 4.40 (br s, 2H), 3.82 (br s, 2H), 3.79 (s, 2H), 3.29 (br s, 2H), 3.13 (br s, 2H), 2.81 (br s, 2H).

EXAMPLE 73

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzenesulfonamide

[0406] This example was made by substituting EXAMPLE 72B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 9.52 (br s, 1H), 8.56 (d, 1H), 8.55 (m, 1H), 7.91 (dd, 1H), 7.84 (m, 2H), 7.76 (d, 2H), 7.67 (tt, 1H), 7.54 (m, 6H), 7.39 (m, 2H), 7.34 (m, 1H), 7.14 (d, 1H), 6.92 (d, 2H), 4.38 (br s, 2H), 3.92 (br s, 2H), 3.78 (s, 4H), 3.26 (br s, 2H), 3.09 (br s, 2H), 2.86 (br s, 2H).

EXAMPLE 74

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide

[0407] This example was made by substituting EXAMPLE 31E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 9.88 (br s, 1H), 8.68 (d, 1H), 8.54 (d, 1H), 7.86 (dd, 1H), 7.76 (d, 2H), 7.72 (m, 1H), 7.50 (m, 4H), 7.46 (m, 2H), 7.41 (d, 1H), 7.37 (m, 2H), 7.26 (m, 2H), 7.07 (t, 2H), 6.97 (t, 1H), 6.92 (d, 2H), 4.73 (quintet, 1H), 4.44 (dd, 1H), 4.31 (dd, 1H), 4.24 (br s, 2H), 4.17 (dd, 1H), 3.75 (m, 2H), 3.24 (br s, 4H), 2.88 (br s, 4H).

EXAMPLE 75A

[0408] This example was made by substituting 5-methylthiophene-2-boronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 75B

[0409] This example was made by substituting EXAMPLE 75A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 75C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(5-methyl-2-thienyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0410] This example was made by substituting EXAMPLE 75B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 10.00 (br s, 1H), 9.58 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.85 (dd, 1H), 7.79 (d, 2H), 7.70 (br s, 1H), 7.47 (m, 3H), 7.23 (d, 2H), 7.18 (m, 2H), 7.14 (m, 2H), 7.03 (d, 1H), 6.97 (d, 2H), 6.86 (m, 1H), 4.40 (br s, 2H), 4.19 (m, 1H), 3.39 (d, 3H), 3.13 (m, 3H), 2.99 (br s, 2H), 2.75 (s, 6H), 2.48 (s, 3H), 2.15 (dd, 2H).

EXAMPLE 76A

[0411] This example was made by substituting EXAMPLE 31C for EXAMPLE 67A in EXAMPLE 67B.

EXAMPLE 76B

[0412] This example was made by substituting EXAMPLE 76A for EXAMPLE 66A in EXAMPLE 66B.

EXAMPLE 76C

[0413] This example was made by substituting EXAMPLE 76B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 76D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfonyl)tetrahydro-3-furanyl)amino)benzenesulfonamide

[0414] This example was made by substituting EXAMPLE 76C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.87 (br s, 1H), 8.50 (d, 1H), 8.48 (d, 1H), 7.82 (d, 2H), 7.77 (dd, 1H), 7.75 (m, 1H), 7.71 (dd, 2H), 7.53 (m, 4H), 7.39 (m, 2H), 7.34 (m, 1H), 7.25 (m, 3H), 7.12 (d, 1H), 6.96 (d, 2H), 4.88 (sextet, 1H), 4.80 (quintet, 1H),4.46 (dd, 1H), 4.28 (br s, 2H), 4.23 (dd, 1H), 4.09 (dd, 1H), 3.86 (dd, 1H), 3.14 (br s, 2H), 2.96 (br s, 4H).

EXAMPLE 77

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfonyl)tetrahydro-3-furanyl)amino)benzenesulfonamide

[0415] This example was made by substituting EXAMPLE 76c for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.90 (br s, 1H), 8.50 (d, 1H), 8.48 (d, 1H), 7.82 (d, 2H), 7.77 (dd, 1H), 7.75 (m, 1H), 7.71 (dd, 2H), 7.52 (m, 2H), 7.48 (t, 2H), 7.42 (t, 1H), 7.36 (m, 2H), 7.23 (m, 3H), 7.12 (d, 1H), 6.96 (d, 2H), 4.88 (sextet, 1H), 4.80 (quintet, 1H),4.46 (dd, 1H), 4.30 (br s, 2H), 4.22 (dd, 1H), 4.09 (dd, 1H), 3.86 (dd, 1H), 3.17 (br s, 2H), 2.89 (br s, 4H).

EXAMPLE 78

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1-methyl-4-(phenylsulfanyl)pyrrolidin-3-yl)amino)-3-nitrobenzenesulfonamide

[0416] This example was made by substituting EXAMPLE 832175D for EXAMPLE 49A in EXAMPLE 49B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (br s, 1H), 10.46 (br s, 1H), 8.60 (d, 1H), 8.49 (d, 1H), 7.95 (dd, 1H), 7.76 (d, 2H), 7.69 (m, 1H), 7.51 (m, 4H), 7.40 (t, 4H), 7.32 (m, 1H), 7.24 (m, 4H), 6.92 (d, 2H), 4.69 (br s, 1H), 4.25 (br s, 2H), 3.97 (br s, 2H), 3.68 (m, 2H), 3.29 (br s, 4H), 2.91 (s, 3H), 2.75 (br s, 2H).

EXAMPLE 79

N-(9-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0417] This example was made by substituting EXAMPLE 837538C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.36 (d, 1H), 7.79 (dd, 1H), 7.72 (d, 2H), 7.36 (d, 2H), 7.28 (d, 2H), 7.21 (t, 2H), 7.15 (d, 1H), 7.12 (d, 2H), 7.03 (d, 1H), 6.84 (d, 2H), 4.13 (m, 1H), 3.52 (m, 4H), 3.38 (m, 4H), 3.21 (br s, 4H), 2.82 (br s, 2H), 2.45 (m, 4H), 2.32 (br s, 4H), 2.20 (br s, 2H), 2.17 (br s, 2H), 2.00 (m, 1H), 1.86 (m, 1H), 1.67 (m, 4H).

EXAMPLE 81A

[0418] This example was made by substituting 4-bromophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 81B

[0419] This example was made by substituting EXAMPLE 81A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 81C

N-(4-(4-((4'-bromo(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0420] This example was made by substituting EXAMPLE 81B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 9.79 (br s, 1H), 9.47 (br s, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.69 (br s, 1H), 7.64 (d, 2H), 7.50 (m, 2H), 7.35 (m, 3H), 7.23 (m, 2H), 7.14 (m, 4H), 6.93 (d, 2H), 4.29 (br s, 2H), 4.19 (m, 1H), 3.77 (br s, 2H), 3.14 (m, 3H), 2.74 (s, 6H), 2.14 (dd, 2H).

EXAMPLE 82A

[0421] 4'-chloro-biphenyl-2-carbonitrile, prepared as described in J. Org. Chem. (1984), 49(9), 1594-1603), (0.35 g) in diethyl ether (25 mL) at -75°C was treated with titanium isopropoxide (0.53 mL) and 3M ethyl magnesium bromide in diethyl ether (1.2 mL), stirred for 10 minutes, stirred at 25°C for 1 hour, treated with BF_3·diethyl etherate (0.41 mL), stirred for 1 hour, treated with 1M HCl (5 mL) then 10% NaOH (15 mL), and extracted with diethyl ether. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel 10%-50% ethyl acetate/hexanes).

EXAMPLE 82B

[0422] A mixture of 4-(bis(2-methanesulfonyloxyethyl)-amino)benzoic acid ethyl ester, prepared as described in J. Med. Chem. (1977), 21(1), 16-26, (80.6 mg), EXAMPLE 82A (58.5 mg), and potassium carbonate (69.1 mg) in acetonitrile (5 mL) in a microwave reactor at 160°C was stirred for 30 minutes, treated with ethyl acetate (10 mL), filtered, and concentrated. The concentrate flash chromatographed on silica gel with 10-30% ethyl acetate/hexanes.

EXAMPLE 82C

[0423] This example was made by substituting EXAMPLE 82B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 82D

N-(4-(4-(1-(4'-chloro(1,1'-biphenyl)-2-yl)cyclopropyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0424] This example was made by substituting EXAMPLE 82C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz,

DMSO-d_6) δ 12.02 (br s, 1H), 9.49 (br s, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.73 (d, 2H), 7.47 (m, 5H), 7.38 (m, 2H), 7.23 (d, 2H), 7.14 (m, 5H), 6.89 (d, 2H), 4.18 (m, 2H), 3.39 (d, 2H), 3.20 (m, 6H), 2.75 (s, 3H), 2.74 (s, 3H), 2.44 (br s, 4H), 2.13 (dd, 2H), 1.01 (br s, 2H), 0.82 (br s, 2H).

EXAMPLE 83A

[0425] A mixture of 2M dimethylamine in THF (27 mL), (R)-2-benzyloxycarbonylamino-3-phenylthiopropionic acid (5.8 g), HoBT (2.67 g), and EDAC·HCl (5.2 g) in THF (50 mL) was stirred for 18 hours at 25°C, treated with water and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 15-50% ethyl acetate/hexanes.

EXAMPLE 83B

[0426] This example was prepared by substituting EXAMPLE 83A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 83C

[0427] This example was prepared by substituting EXAMPLE 83B for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 83D

[0428] This example was prepared by substituting EXAMPLE 83C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 83E

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(dimethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0429] This example was made by substituting EXAMPLE 837538C and EXAMPLE 83D for EXAMPLE 2C and 4-(((lR)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.46 (br s, 1H), 9.36 (br s, 1H), 8.52 (d, 1H), 8.28 (d, 1H), 7.88 (dd, 1H), 7.79 (d, 2H), 7.41 (d, 2H), 7.35 (d, 2H), 7.17 (m, 4H), 7.09 (m, 2H), 6.96 (d, 2H), 4.67 (m, 1H), 3.89 (br s, 2H), 3.75 (m, 4H), 3.43 (m, 2H), 3.36 (m, 4H), 3.16 (br s, 2H), 2.82 (s, 3H), 2.75 (s, 3H), 2.26 (br s, 2H), 2.21 (br s, 2H), 1.71 (br s, 4H).

EXAMPLE 84

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(dimethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0430] This example was made by substituting EXAMPLE 83D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 9.94 (br s, 1H), 9.42 (br s, 1H), 8.51 (d, 1H), 8.28 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.73 (br s, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.34 (m, 2H), 7.17 (m, 2H), 7.09 (m, 3H), 6.93 (d, 2H), 4.66 (m, 1H), 4.29 (br s, 2H), 3.85 (br s, 2H), 3.75 (t, 2H), 3.43 (d, 2H), 3.36 (m, 2H), 3.12 (br s, 4H), 2.87 (br s, 3H), 2.82 (s, 3H).

EXAMPLE 85A

[0431] This example was prepared by substituting diethylamine for dimethylamine in EXAMPLE 83A.

EXAMPLE 85B

[0432] This example was prepared by substituting EXAMPLE 85A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 85C

[0433] This example was prepared by substituting EXAMPLE 85B for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 85D

[0434] This example was prepared by substituting EXAMPLE 85C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 85E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0435] This example was made by substituting EXAMPLE 85D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 9.99 (br s, 1H), 9.02 (br s, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.74 (br s, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.33 (m, 2H), 7.18 (m, 2H), 7.10 (m, 3H), 6.93 (d, 2H), 4.60 (m, 1H), 4.26 (br s, 2H), 3.85 (br s, 2H), 3.43 (m, 2H), 3.36 (dd, 2H), 3.15 (m, 6H), 2.92 (br s, 4H), 1.19 (m, 6H).

EXAMPLE 86A

[0436] This example was prepared by substituting morpholine for dimethylamine in EXAMPLE 83A.

EXAMPLE 86B

[0437] This example was prepared by substituting EXAMPLE 86A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 86C

[0438] This example was prepared by substituting EXAMPLE 86B for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 86D

[0439] This example was prepared by substituting EXAMPLE 86C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 86E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0440] This example was made by substituting EXAMPLE 86D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 9.95 (br s, 1H), 8.51 (d, 1H), 8.33 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.74 (br s, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.34 (m, 1H), 7.25 (d, 1H), 7.19 (m, 2H), 7.09 (m, 3H), 6.93 (d, 2H), 4.59 (br s, 1H), 4.29 (br s, 2H), 3.39 (m, 4H), 3.12 (br s, 6H), 2.90 (br s, 3H).

EXAMPLE 87

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(diethylamino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0441] This example was made by substituting EXAMPLE 837538C and EXAMPLE 85D for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (br s, 1H), 9.67 (br s, 1H), 9.06 (br s, 1H), 8.52 (d, 1H), 8.33 (d, 1H), 7.87 (dd, 1H), 7.79 (d, 2H), 7.41 (d, 2H), 7.33 (d, 1H), 7.17 (m, 4H), 7.10 (m, 3H), 6.96 (d, 2H), 4.61 (m, 1H), 3.88 (br s, 2H), 3.76 (m, 4H), 3.59 (br s, 2H), 3.42 (m, 2H), 3.15 (m, 4H), 2.80 (br s, 2H), 2.27 (br s, 2H), 2.22 (br s, 2H), 1.71 (br s, 4H), 1.19 (dd, 6H).

EXAMPLE 88

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0442] This example was made by substituting EXAMPLE 837538C and EXAMPLE 86D for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.97 (br s, 1H), 9.55 (br s, 1H), 8.51 (d, 1H), 8.38 (d, 1H), 7.86 (dd, 1H), 7.79 (d, 2H), 7.41 (d, 2H), 7.25 (d, 1H), 7.17 (m, 5H), 7.09 (m, 2H), 6.96 (d, 2H), 4.58 (m, 1H), 3.90 (br s, 2H), 3.39 (m, 4H), 3.17 (br s, 4H), 2.80 (br s, 2H), 2.26 (br s, 2H), 2.22 (br s, 2H), 1.71 (br s, 4H).

EXAMPLE 89

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0443] A mixture of EXAMPLE 833566 (44.9 mg) and 2.47 mmol/g MP-BH_3CN (0.81 g) in 1:1 dichloromethane/methanol at 25°C (4 mL) was treated with DIEA and acetic acid to pH 5-6, shaken for 18 hours, filtered, and concentrated. The concentrate was chromatographed on C-18 with 30-100% acetonitrile/water/0.1% TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.13 (br s, 1H), 9.76 (br s, 1H), 9.18 (br s, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.71 (br s, 1H), 7.53 (m, 4H), 7.41 (d, 2H), 7.34 (m, 1H), 7.23 (m, 3H), 7.14 (m, 3H), 6.93 (d, 2H), 4.33 (br s, 2H), 4.22 (m, 1H), 3.85 (br s, 2H), 3.12 (m, 4H), 2.82 (s, 3H), 2.19 (m, 2H), 0.81 (m, 4H).

EXAMPLE 90A

[0444] A mixture of magnesium turnings (0.144 g) and one iodine crystal at 25°C was treated with 2-phenylbenzyl bromide (1.48 g) in diethyl ether (10 mL), stirred for 3 hours, cooled to 0°C, treated with 4-(4-oxo-piperidine-1-yl)benzoic acid ethyl ester, prepared as described in J. Het. Chem. 1969, 6, 941, (1.48 g) in diethyl ether (5 mL) and THF (5 mL), stirred at 25°C for 18 hours, and treated with ethyl acetate and aqueous NH_4Cl. The extract was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 25% ethyl acetate/hexane.

EXAMPLE 90B

[0445] EXAMPLE 90A (0.27 g) in THF (10 mL) at 25°C was treated with 60% oily NaH (0.24 g), stirred for 2 hours at 50°C, treated with HMPA (2 mL) and methyl iodide (2 mL), heated at reflux for 18 hours, cooled to 0°C, and treated with ethyl acetate and aqueous $NaHSO_4$. The extract was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 90C

[0446] A mixture of EXAMPLE 90B (0.09 g) and 1M LiOH (1 mL) in dioxane (5 mL) at 60°C was stirred for 18 hours, and concentrated. The concentrate in water was treated with 2M HCl and filtered.

EXAMPLE 90D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0447] This example was made by substituting EXAMPLE 90C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.95 (br s, 1H), 9.38 (s, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.70 (d, 2H), 7.30 (m, 10H), 7.15 (m, 4H), 6.82 (d, 2H), 4.19 (m, 1H), 3.45 (m, 4H), 3.13 (m, 2H), 3.04 (s, 3H), 2.88 (m, 4H), 2.74 (d, 6H), 2.14 (q, 2H), 1.47 (m, 2H), 1.18 (m, 2H).

EXAMPLE 91A

[0448] A mixture of magnesium turnings (0.432 g) and one iodide crystal at 25°C was treated with 2-bromobenzyl

bromide (4.5 g) in diethyl ether (30 mL), stirred for 3 hours, cooled to 0°C, treated with 4-(4-oxo-piperidine-1-yl)benzoic acid ethyl ester, prepared as described in J. Het. Chem. 1969, 6, 941, (3.7 g) in diethyl ether (20 mL) and THF (10 mL), stirred at 25°C for 18 hours, and treated with ethyl acetate and aqueous NH_4Cl. The extract was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexane.

EXAMPLE 91B

[0449] EXAMPLE 91A (1.6 g) in THF (20 mL) at 25°C was treated with 60% oily NaH (0.288 g), stirred for 2 hours at 50°C, treated with HMPA (3 mL) and methyl iodide (3 mL), stirred at reflux for 18 hours, cooled to 0°C, and treated with ethyl acetate and aqueous $NaHSO_4$. The extract was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10-15% ethyl acetate/hexanes.

EXAMPLE 91C

[0450] A mixture of EXAMPLE 91B (0.6 g) and 1M LiOH (5 mL) in dioxane (5 mL) at 60°C was stirred for 18 hours and concentrated. The concentrate in water was treated with 2M HC, and filtered.

EXAMPLE 91D

[0451] This example was made by substituting EXAMPLE 91C for EXAMPLE 2C in EXAMPLE 2D.

EXAMPLE 91E

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-methoxy-4-(2-(pyridin-3-yl)benzyl)piperidin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0452] A mixture of EXAMPLE 91D (0.08 g), 3-pyridineboronic acid (0.04 g), $Pd(dppf)_2Cl_2$ (0.01 g),and Cs_2CO_3 (0.1 g) in DMF (1 mL) at 80°C was stirred for 2 days and treated with ethyl acetate and brine. The extract was extracted with ethyl acetate, and the extracts were combined and dried (Na_2SO_4), filtered, and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.64 (d, 2H), 8.54 (d, 1H), 8.28 (d, 1H), 7.97 (dd, 1H), 7.86 (dd, 1H), 7.70 (d, 2H), 7.62 (m, 1H), 7.37 (m, 3H), 7.23 (m, 3H), 7.13 (m, 4H), 6.83 (d, 2H), 4.19 (m, 1H), 3.45 (m, 2H), 3.39 (d, 2H), 3.13 (m, 2H),2.99 (s, 3H), 2.88 (m, 4H), 2.74 (d, 6H), 2.14 (q, 2H), 1.49 (d, 2H), 1.20 (dt, 2H).

EXAMPLE 92

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-methoxy-4-(2-(pyridin-4-yl)benzyl)piperidin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0453] This example was prepared by substituting 4-pyridineboronic acid for 3-pyridineboronic acid in EXAMPLE 91. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.47 (br s, 1H), 8.75 (d, 2H), 8.53 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.70 (d, 2H), 7.66 (d, 2H), 7.39 (m, 3H), 7.23 (d, 2H), 7.13 (m, 4H), 6.83 (d, 2H), 4.18 (m, 1H), 3.46 (m, 2H), 3.39 (d, 2H), 3.13 (m, 2H),2.99 (s, 3H), 2.86 (m, 4H), 2.74 (d, 6H), 2.14 (q, 2H), 1.49 (d, 2H), 1.20 (dt, 2H).

EXAMPLE 93

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-methoxy-4-(2-(2-thienyl)benzyl)piperidin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0454] This example was prepared by substituting thiophene-2-boronic acid for 3-pyridineboronic acid in EXAMPLE 91. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.44 (d, 1H), 8.26 (d, 1H), 7.79 (dd, 1H), 7.67 (d, 2H), 7.57 (dd, 1H), 7.3 (m, 8 H), 7.17 (d, 1H), 7.10 (m, 2H), 6.87 (d, 1H),6.71 (d, 2H), 4.05 (m, 1H), 3.30 (m, 4H), 3.12 (s, 3H), 3.03 (s, 2H), 2.74 (m, 4H), 2.43 (s, 6H), 2.00 (m, 2H), 1.55 (d, 2H), 1.30 (dt, 2H).

EXAMPLE 94

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-methoxy-4-(2-(3-thienyl)benzyl)piperidin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0455] This example was prepared by substituting thiophene-3-boronic acid for 3-pyridineboronic acid in EXAMPLE 91. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.44 (d, 1H), 8.26 (d, 1H), 7.79 (dd, 1H), 7.67 (d, 2H), 7.59 (m, 1H), 7.44 (m, 1H), 7.28 (m, 7H), 7.16 (m, 2H), 6.87 (d, 1H),6.71 (d, 2H), 4.05 (m, 1H), 3.30 (m, 4H), 3.07 (s, 3H), 2.94 (s, 2H), 2.74 (m, 4H), 2.45 (s, 6H), 2.00 (m, 2H), 1.49 (d, 2H), 1.25 (dt, 2H).

EXAMPLE 95A

[0456] N-methyl-2,2,2-trifluoroacetamide (6.35 g) in diethyl ether (25 mL) at - 15°C was treated with lithium aluminum hydride (3.8 g) in diethyl ether (25 mL) over 1 hour, stirred for 2 hours, stirred at 25°C for 16 hours, cooled to 0°C, treated with water, and distillated at 34-36°C. The distillate was treated with HCl and filtered.

EXAMPLE 95B

4-(((1R)-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0457] This example was made by substituting EXAMPLE 95A for isopropylamine in EXAMPLE 28. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.67 (d, 1H), 8.52 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.52 (d, 1H), 7.47 (m, 4H), 7.38 (m, 2H), 7.24 (m, 2H), 7.14 (m, 4H), 6.82 (d, 2H), 4.46 (m, 1H), 4.12 (q, 2H), 3.35 (m, 10H), 3.04 (s, 3H), 2.42 (m, 4H). EXAMPLE 96A

[0458] This example was made by substituting 2,2,2-trifluoroethylamine for isopropylamine in EXAMPLE 28.

EXAMPLE 96

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((2,2,2-trifluoroethyl)amino)propyl)amino)benzenesulfonamide

[0459] Borane·dimethyl sulfide (0.37 mL) was treated with EXAMPLE 96A (110 mg) in THF (2 mL) at 25°C, for 5 hours, treated with methanol, and concentrated. The concentrate was purified by HPLC with 0-70% acetonitrile/water/ 0.1% TFA. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.53 (d, 1H), 8.30 (d, 1H), 7.84 (dd, 1H), 7.76 (d, 2H), 7.52 (m, 3H), 7.35 (m, 4H), 7.15 (m, 6H), 6.92 (d, 2H), 4.46 (m, 1H), 3.75 (m, 2H), 3.5 (m, 12H), 2.42 (m, 4H).

EXAMPLE 97A

[0460] This example was made by substituting methyl trifluoroacetamide for EXAMPLE 100A in EXAMPLE 100B.

EXAMPLE 97B

[0461] This example was made by substituting EXAMPLE 97A and EXAMPLE 30A for isopropylamine and EXAMPLE 27E in EXAMPLE 28.

EXAMPLE 97C

[0462] This example was made by substituting EXAMPLE 97B for EXAMPLE 96A in EXAMPLE 96.

EXAMPLE 97D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0463] This example was made by substituting EXAMPLE 97C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.72 (d, 1H), 8.59 (d, 1H), 7.99 (dd, 1H), 7.95 (d, 2H), 7.71 (m, 3H), 7.55 (m, 3H), 7.41 (d, 2H), 7.29 (m, 5H), 7.11 (d, 2H), 4.46 (br s, 1H), 4.33 (m, 1H), 3.75 (m, 12H), 3.31 (q, 2H), 2.78 (m, 2H), 2.68 (s, 3H), 2.09 (m, 2H).

EXAMPLE 98

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0464] This example was made by substituting EXAMPLE 32D and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.71 (s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.69 (d, 2H), 7.46 (d, 2H), 7.30 (m, 7H), 7.14 (m, 4H), 6.82 (d, 2H), 4.18 (m, 1H), 3.95 (m,2H), 3.67 (m, 4H), 3.39 (m, 4H), 3.19 (m, 2H), 3.03 (s, 3H), 3.00 (m, 2H), 2.85 (m, 4H), 2.17 (m, 2H), 1.47 (d, 2H), 1.17 (t, 2H).

EXAMPLE 99

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0465] This example was made by substituting EXAMPLE 32D and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.74 (t, 1H), 8.53 (d, 1H), 7.90 (dd, 1H), 7.68 (d, 2H), 7.46 (d, 2H), 7.46 (m, 3H), 7.28 (m, 6H), 7.16 (m, 3H), 6.81 (d, 2H), 3.66 (q, 2H) 3.41 (m, 2H), 3.03 (s, 3H), 2.48 (m, 4H), 1.47 (m, 2H), 1.18 (dt, 2H).

EXAMPLE 100A

[0466] Trifluoroacetic anhydride (15 g) in diethyl ether (80 mL) at -10°C was treated with ethylamine for 40 minutes and distilled under vacuum at 68°C.

EXAMPLE 100B

[0467] EXAMPLE 100A (7.8 g) in diethyl ether (25 mL) at -15°C was treated with lithium aluminum hydride (4.17 g) in diethyl ether (25 mL) over 1 hour, stirred for 2 hours then at 25°C for 16 hours, cooled to 0°C, treated with water (10 mL), 15% NaOH (10 mL), and water (30 mL), stirred a for 30 minutes, and filtered. The filtrate was washed with water and brine, dried (Na_2SO_4), and filtered. The filtrate was treated with HCl, and filtered.

EXAMPLE 100C

[0468] This example was made by substituting EXAMPLE 100B and EXAMPLE 30A for isopropylamine and EXAMPLE 27E in EXAMPLE 28.

EXAMPLE 100D

[0469] This example was made by substituting EXAMPLE 100C for EXAMPLE 96A in EXAMPLE 96.

EXAMPLE 100E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(ethyl(2,2,2-trifluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0470] This example was made by substituting EXAMPLE 100D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.90 (br s, 1H), 8.51 (d, 1H), 8.32 (d, 1H), 7.80 (dd, 1H), 7.74 (d, 2H), 7.46 (m, 5H), 7.37 (m, 2H), 7.24 (d, 2H), 7.12 (m, 3H), 7.02 (d, 1H), 6.89 (d, 2H), 4.12 (m, 1H), 3.42 (s, 2H), 3.35 (m, 6H), 3.13 (q, 2H), 2.63 (t, 2H), 2.56 (q, 2H), 2.40 (s, 4H), 1.90 (m, 2H), 0.88 (t, 3H).

EXAMPLE 101

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-fluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0471] This example was made by substituting 2-fluoroethylamine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.80 (s, 2H), 8.53 (d, 1H), 8.26 (d, 1H), 7.86 (dd, 1H), 7.75 (m, 3H), 7.52 (m, 4H), 7.38 (d, 2H), 7.33 (m, 1H), 7.15 (m, 5H), 6.92 (d, 2H), 4.71 (t, 1H), 4.61 (t, 1H), 4.30 (m, 2H), 4.21 (m, 1H), 3.38 (d, 2H), 3.25 (m, 12H), 2.11 (m, 2H).

EXAMPLE 102

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2,2-difluoroethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0472] This example was made by substituting 2,2-difluoroethylamine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.15 (s, 2H), 8.53 (d, 1H), 8.26 (d, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (m, 4H), 7.38 (d, 2H), 7.33 (m, 1H), 7.15 (m, 5H), 6.92 (d, 2H), 6.36 (tt, 1H), 4.23 (m, 1H), 4.00 (m, 4H), 3.49 (t, 2H), 4.39 (d, 2H), 3.10 (m, 4H), 2.90 (m, 2H), 2.54 (s, 2H), 2.13 (m, 2H).

EXAMPLE 103A

[0473] A mixture of EXAMPLE 2 (250 mg) and 10% Pd on carbon (100 mg) in methanol (5 mL) and ethyl acetate (5 mL) at 25°C was stirred under H_2 (balloon) for 18 hours, filtered through diatomaceous earth (Celite®), and concentrated.

EXAMPLE 103B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-1H-benzimidazole-5-sulfonamide

[0474] A mixture of EXAMPLE 103A (0.06 g) in 80% formic acid (3 mL) at 100°C was stirred for 3 hours and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.01 (s, 1H), 9.64 (s, 1H), 8.56 (s, 1H), 8.22 (s, 1H), 7.83 (d, 1H), 7.75 (m, 4H), 7.52 (m, 4H), 7.40 (d, 2H), 7.33 (m, 1H), 7.14 (m, 3H), 7.07 (m, 1H), 6.92 (d, 2H), 4.76 (m, 1H), 3.85 (m, 6H), 3.66 (d, 2H), 3.15 (m, 4H), 2.71 (s, 6H), 2.45 (m, 2H).

EXAMPLE 104

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)-1H-1,2,3-benzotriazole-5-sulfonamide

[0475] A mixture of EXAMPLE 103A (0.06 g) and 12M HCl (0.56 mL) in acetic acid (2 mL) at 0°C was treated with $NaNO_2$ (7.2 mg) in water (0.38 mL), stirred for 2 hours, and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.57 (s, 1H), 8.06 (d, 1H), 7.99 (d, 1H), 7.77 (d, 2H), 7.74 (m, 1H), 7.52 (m, 4H), 7.40 (d, 2H), 7.33 (m, 1H), 7.04 (m, 5H), 6.92 (d, 2H), 5.24 (m, 1H), 3.74 (m, 2H), 3.45 (m, 6H), 3.15 (m, 4H), 2.71 (s, 6H).

EXAMPLE 105A

[0476] 3-Cyano-4-fluorobenzenesulfonyl chloride (5 g) in dichloromethane (110 mL) at -78 °C was treated with 7M NH_3 in methanol (8.1 mL), stirred at -20 °C, and acidified with 1M HCl. The water layer was separated and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was recrystallized from hexane/ethyl acetate.

EXAMPLE 105B

[0477] This example was made by substituting EXAMPLE 18C with EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 105B

[0478] A mixture of EXAMPLE 105A (0.5 g), EXAMPLE 105B (0.5 g), and DIEA (0.8 mL) in THF (6 mL) at 80°C was stirred for 16 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane.

EXAMPLE 105C

[0479] A mixture of EXAMPLE 105B (0.05 g) and KOH (0.031 g) in tert-butanol (2 mL) at reflux was stirred for 6 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5-10% methanol/dichloromethane.

EXAMPLE 105D

5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzamide

[0480] This example was made by substituting EXAMPLE 105C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.82 (s, 1H), 9.63 (s, 1H), 8.82 (d, 1H), 8.15 (s, 1H), 7.76 (d, 2H), 7.70 (d, 1H), 7.52 (d, 4H), 7.39 (d, 2H), 7.33 (m, 2H), 7.27 (m, 2H), 7.19 (m, 1H), 6.92 (d, 2H), 6.69 (s, 1H), 4.14 (m, 1H), 3.86 (m, 2H), 3.45 (m, 6H), 3.15 (m, 4H), 2.74 (s, 6H), 2.10 (m, 1H), 1.96 (m, 1H).

EXAMPLE 106B

[0481] A mixture of EXAMPLE 1A (1.5 g), 2-bromobenzoyl chloride (1.5 g), and DIEA (2 mL) in THF (20 mL) at 25°C was stirred for 16 hours, filtered, and concentrated.

EXAMPLE 106C

[0482] EXAMPLE 106B (0.3g), 4-(N,N-dimethylamino)phenylboronic acid (0.146 g), $PdCl_2(PPh_3)_4$ (0.03 g), and 2M Na_2CO_3 (0.4 mL) in 7:3:2 DME/water/ethanol (3 mL) at 150°C in a 10 mL microwave reaction tube was stirred in a microwave reactor for 20 minutes, filtered through diatomaceous earth (Celite®) and concentrated. The concentrate was flash chromatographed on silica gel with 5-50% ethyl acetate/hexanes.

EXAMPLE 106D

[0483] This example was made by substituting EXAMPLE 106C for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 106E

N-(4-(4-((4'-(dimethylamino)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0484] This example was made by substituting EXAMPLE 106D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.01 (s, 1H), 9.29 (s, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.30 (m, 11H), 6.80 (d, 2H), 6.73 (d, 2H), 4.18 (m, 1H), 3.50 (m, 4H), 3.39 (m, 4H), 3.04 (m, 6H), 2.78 (s, 6H), 2.74 (d, 6H), 2.14 (m, 2H).

EXAMPLE 107A

[0485] This example was prepared by substituting 4-(methylsulfanyl)phenylboronic acid for 4-(N,N-dimethylamino)phenylboronic acid in EXAMPLE 106C.

EXAMPLE 107B

[0486] This example was made by substituting EXAMPLE 107A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 107C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0487] This example was made by substituting EXAMPLE 107B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.01 (s, 1H), 9.38 (s, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.49 (m, 3H), 7.33 (m, 5H),7.17 (m, 5H), 6.83 (d, 2H), 4.18 (m, 1H), 3.65 (m, 2H), 3.39 (m, 4H), 3.11 (m, 4H), 2.97 (m, 1H), 2.85 (m, 1H), 2.73 (d, 6H), 2.39 (s, 3H), 2.14 (m, 2H).

EXAMPLE 108A

[0488] This example was prepared by substituting 4-chlorophenylboronic acid for 4-(N,N-dimethylamino)phenylboronic acid in EXAMPLE 106C.

EXAMPLE 108B

[0489] This example was made by substituting EXAMPLE 108A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 108C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfanyl)(1,1'-biphenyl)-2-yl)carbonyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0490] This example was made by substituting EXAMPLE 108B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.01 (s, 1H), 9.38 (s, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.74 (d, 2H), 7.49 (m, 8H), 7.17 (m, 5H), 6.83 (d, 2H), 4.18 (m, 1H), 3.65 (m, 2H), 3.39 (m, 4H), 3.11 (m, 4H), 2.99 (m, 1H), 2.89 (m, 1H), 2.74 (d, 6H), 2.14 (m, 2H).

EXAMPLE 109

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-cyano-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0491] This example was made by substituting EXAMPLE 105B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.70 (s, 1H), 9.60 (s, 1H), 7.68 (d, 1H), 7.52 (d, 2H), 7.27 (m, 43H), 7.14 (d, 2H), 7.08 (m, 1H), 7.00 (m, 5H), 6.91 (m, 1H), 6.67 (d, 2H), 6.37 (m, 2H), 3.96 (m, 1H), 3.70 (m, 2H), 3.80 (m, 4H),3.02 (m, 4H), 2.89 (m, 4H), 2,58 (s, 6H), 1.84 (m, 2H).

EXAMPLE 110A

[0492] 3,4-dihydroxy-butyric acid methyl ester, prepared as described in Chem. Lett., 1984, 1389, (510 mg) in dimethylamine in THF (19 mL) in a sealed tube at 80°C was stirred for 12 hours and concentrated. The concentrate was flash chromatographed on silica gel with 0-20% methanol/dichloromethane.

EXAMPLE 110B

[0493] A mixture of EXAMPLE 110A (200 mg), benzenethiol (153 μL), and tributylphosphine (372 μL) in THF (10 mL) at 0°C was treated with 1,1'-(azodicarbonyl)dipiperidine (377 mg), stirred at 25°C for 12 hours, and treated with ethyl acetate and 1M NaOH. The extract was extracted with ethyl acetate, and the extract was dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 0% to 80% ethyl acetate/dichloromethane.

EXAMPLE 110C

[0494] EXAMPLE 110B (160 mg) in THF (2.3 mL) at 25°C was treated with borane·THF (1 mL), stirred for 5 hours, treated with saturated methanolic HCl (3 mL), heated at reflux for 2 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 0-10% NH_3-saturated methanol (saturated NH_3)/dichloromethane.

EXAMPLE 110D

[0495] EXAMPLE 110C (224 mg) in DMF (1 mL) at 0°C was treated with NaH (40 mg), stirred at 25°C for 1 hour, cooled to 0°C, treated with 15-crown-5 (146 μL), stirred for 15 minutes, treated with 4-fluoro-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, (110 mg), stirred at 25°C for 2 hours, treated with saturated NH_4Cl (200 μL), and concentrated. The concentrate was flash chromatographed on silica gel with 50-100% ethyl acetate/hexane then switching to 0-10% NH_3-saturated methanol/dichloromethane.

EXAMPLE 110E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)oxy)-3-nitrobenzenesulfonamide

[0496] This example was made by substituting EXAMPLE 110D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.70 (s, 1H), 8.38 (d, 1H), 8.09 (dd, 1H), 7.78 (m, 3H), 7.51 (m, 5H), 7.27 (m, 8H), 6.92 (d, 2H), 5.01 (m, 1H), 3.47 (m, 2H), 3.33 (m, 2H), 3.21 (m, 4H), 3.14 (m, 2H), 3.05 (s, 2H), 2.76 (s, 6H), 2.23 (m, 2H).

EXAMPLE 111

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0497] This example was made by substituting 4,4-dimethyl-4,5-dihydro-1H-imidazole for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.29 (s, 1H), 8.54 (d, 1H),8.29 (s, 1H), 7.86 (dd, 1H), 7.76 (d, 2H),7.65 (m, 2H), 7.46 (m, 5H), 7.30 (m, 1H), 7.22 (d, 2H), 7.12 (m, 4H), 6.92 (d, 2H), 4.14 (m, 1H), 3.54 (m, 4H), 3.40 (m, 10H), 2.18 (m, 2H), 1.32 (s, 6H), 0.87 (m, 2H).

EXAMPLE 112

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0498] This example was made by substituting 1,4,5,6-tetrahydro-pyrimidine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.09 (s, 1H), 9.62 (d, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 8.02 (d, 1H), 7.85 (dd, 1H), 7.76 (d, 2H),7.51 (m, 3H), 7.40 (m, 1H), 7.14 (m, 7H), 6.93 (d, 2H), 4.14 (m, 1H), 3.40 (m, 14H),3.19 (m, 2H), 2.12 (m, 2H), 1.88 (m, 2H).

EXAMPLE 113

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0499] This example was made by substituting 2-methyl-4,5-dihydro-1H-imidazole for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.56 (d, 1H), 8.32 (d, 1H), 7.90 (dd, 1H), 7.81 (d, 2H),7.55 (m, 4H), 7.43 (d, 2H), 7.37 (m, 1H), 7.26 (m, 3H), 7.14 (m, 3H), 6.97 (d, 2H), 4.28 (m, 2H), 3.85 (m, 14H),3.42 (m, 2H), 2.14 (m, 2H), 2.08 (s, 3H), 1.27 (m, 2H).

EXAMPLE 114

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(5,6-dihydro-1(4H)-pyrimidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0500] This example was made by substituting EXAMPLE 842657F and 1,4,5,6-tetrahydro-pyrimidine for isopropylamine and 35A in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.60 (s, 1H), 8.01 (d, 1H), 7.95 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 2H),7.68 (m, 1H), 7.49 (m, 3H), 7.41 (d, 2H), 7.27 (m, 5H), 7.17 (m, 1H), 6.90 (d, 2H), 6.82 (d, 1H), 6.00 (d, 1H), 3.83 (m, 2H), 3.40 (m, 16H), 2.08 (m, 2H), 1.285 (t, 2H).

EXAMPLE 115

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0501] This example was made by substituting 2,4-dimethyl-4,5-dihydro-1H-imidazole for 1,4,5,6-tetrahydro-pyrimidine In EXAMPLE 114. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.92 (s, 1H), 10.02 (s, 1H), 7.95 (d, 1H), 7.82 (dd, 1H), 7.73 (d, 2H),7.70 (m, 1H), 7.50 (m, 3H), 7.40 (d, 2H), 7.27 (m, 5H), 6.92 (m, 3H), 6.04 (d, 1H), 4.08 (m, 2H), 3.90 (m, 4H), 3.40 (m, 10H), 2.04 (m, 2H), 2.02 (s, 3H), 1.10 (m, 3H).

EXAMPLE 116

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2-methyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0502] This example was made by substituting 2-methyl-4,5-dihydro-1H-imidazole for 1,4,5,6-tetrahydro-pyrimidine In EXAMPLE 114. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.82 (s, 1H), 7.88 (d, 1H), 7.75 (dd, 1H), 7.68 (d, 2H),7.62 (m, 1H), 7.43 (m, 3H), 7.35 (d, 2H), 7.28 (m, 5H), 6.82 (m, 3H), 5.98 (d, 1H), 3.90 (m, 2H), 3.70 (m, 4H), 3.40 (m, 12H), 2.00 (m, 2H), 1.95 (s, 3H).

EXAMPLE 117

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4,4-dimethyl-4,5-dihydro-1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0503] This example was made by substituting 4,4-dimethyl-4,5-dihydro-1H-imidazole for 1,4,5,6-tetrahydro-pyrimidine In EXAMPLE 114. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.92 (s, 1H), 10.22 (s, 1H),8.25 (d, 1H), 7.95 (d, 1H), 7.80 (dd, 1H), 7.75 (d, 2H),7.65 (m, 1H), 7.52 (m, 3H), 7.50 (d, 2H), 7.25 (m, 5H), 7.18 (m, 1H), 6.90 (d, 2H), 6.82 (d, 1H), 6.00 (d, 1H), 3.88 (m, 2H), 3.50 (m, 4H), 3.40 (m, 10H), 2.08 (m, 2H), 1.25 (m, 6H).

EXAMPLE 118A

[0504] EXAMPLE 18D (200 mg), cesium carbonate (671 mg) and tetrabutylammonium iodide (61 mg) in DMF (4 mL) at 25°C was treated with 4-methoxybenzyl chloride (246 μL), stirred for 12 hours, and treated with ethyl acetate and saturated NH_4Cl. The extract was extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-50% ethyl acetate/hexane.

EXAMPLE 118B

[0505] EXAMPLE 110C (38 mg) in N-methyl-2-pyrrolidinone (845 μL) at 25°C was treated with NaH (8 mg), stirred for 20 minutes, treated with EXAMPLE 118A (122 mg), stirred for 3 hours, treated with NaH (6.6 mg) and EXAMPLE 118A (76 mg), stirred for 3 hours, treated with saturated $NaHCO_3$, (1 mL), and partitioned between ethyl acetate and saturated $NaHCO_3$. The extract was extracted with ethyl acetate, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-to 50% acetonitrile (1% NH_3-saturated methanol)/1% NH_3-saturated ethyl acetate.

EXAMPLE 118C

[0506] EXAMPLE 118C (90 mg) in triethylsilane/TFA/dichloromethane (0.05 mL/0.45 mL/0.5 mL) at 25°C was stirred for 12 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5% NH_3-saturated methanol/dichloromethane.

EXAMPLE 118D

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)oxy)-3-(trifluoromethyl)benzenesulfonamide

[0507] This example was made by substituting EXAMPLE 118C and EXAMPLE 837538C for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide (prepared according to the procedure described in commonly owned WO02/24636, filed September 20, 2001) in EXAMPLE 2D. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.40 (s, 1H),8.12 (d, 2H), 7.72 (d, 2H), 7.41 (m, 3H), 7.31 (d, 2H),7.26 (m, 2H), 7.17 (m, 3H), 6.95 (d, 2H), 4.97 (m, 1H), 3.50 (m, 12H), 3.16 (m, 4H), 2.76 (s, 6H), 2.23 (m, 4H), 1.70 (s, 4H).

EXAMPLE 119A

[0508] A mixture of 4-bromo-3-(trifluoromethyl)benzenesulfonamide (0.121 g), EXAMPLE 847124C (0.17g) EDAC (0.153 g), and DMAP (0.098g) in dichloromethane (2 mL) at 25°C was stirred for 16 hours, treated with ethyl acetate, washed with saturated NH_4Cl solution and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane.

EXAMPLE 119B

N-(4-(4-((2-(4-chlorophenyl)cyclohept-1-en-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0509] A mixture of EXAMPLE 119A (0.1 g), EXAMPLE 105B (0.038 g), $Pd_2(dba)_3$ (0.011g), BINAP (0.009g), Cs_2CO_3 (0.07g) in toluene (1.5 mL) at 100°C was stirred for 16 hours, filtered, and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm $\times$ 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.60 (s, 1H), 7.95 (d, 1H), 7.81 (dd, 1H), 7.76 (d, 2H), 7.41 (d, 2H), 7.28 (m,4H), 7.12 (d, 2H), 6.94 (d, 2H), 6.87 (d, 1H), 6.02 (d, 1H), 3.91 (m, 3H), 3.63 (m, 2H), 3.40 (m, 2H), 3.28 (m, 2H), 3.15 (m, 4H), 3.00 (m, 2H), 2.73 (d, 6H), 2.46 (m, 4H), 2.10 (m, 2H), 1.82 (m, 2H), 1.57 (m, 4H).

EXAMPLE 120

4-(((1R)-3-(bis(2-methoxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0510] This example was made by substituting bis(2-methoxyethyl)amine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.50 (s, 1H), 8.54 (d, 1H),8.27 (d, 1H), 7.87 (dd, 1H), 7.77 (m, 3H), 7.52 (m, 4H), 7.39 (d, 2H), 7.34 (m, 1H), 7.16 (m, 5H), 6.94 (d, 2H), 4.32 (m, 1H), 4.20 (m, 2H), 3.61 (m, 4H), 3.39 (m, 2H), 3.30 (m, 12), 3.23 (s, 6H), 2.17 (m, 2H).

EXAMPLE 121

4-(((1R)-3-(bis(2-methoxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(trifluoromethyl)benzenesulfonamide

[0511] This example was made by substituting bis(2-methoxyethyl)amine for 1,4,5,6-tetrahydropyrimidine in EXAMPLE 114. ^{1}H NMR (500MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.50 (s, 1H), 7.95 (d, 1H),7.83 (dd, 1H), 7.75 (m, 3H), 7.53 (m, 4H), 7.39 (d, 2H), 7.34 (m, 5H), 7.16 (m, 1H), 6.94 (m, 2H), 6.02 (d, 1H), 4.32 (m, 1H), 3.96 (m, 2H), 3.61 (m, 4H), 3.39 (m, 16H), 3.23 (s, 6H), 2.17 (m, 2H).

EXAMPLE 122A

[0512] A mixture of EXAMPLE 29C (0.5g) and diethylamine (4 mL) in THF (4 mL) at 25°C was stirred for 2 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5% to 10% methanol/dichloromethane.

EXAMPLE 122B

4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-4-yl)methyl)-1-piperazinyl)benzoyl)-3-nitrobenzenesulfonamide (doesn't match structure - lacks trifluorophenyl, bears bis isopropylamino)

[0513] This example was made by substituting EXAMPLE 122A for EXAMPLE 105B EXAMPLE 119B. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.02 (s, 1H), 9.60 (s, 1H), 8.50 (s, 1H), 7.95 (d, 1H), 7.81 (dd, 1H), 7.76 (d, 2H), 7.41 (d, 2H), 7.28 (m,4H), 7.12 (d, 2H), 6.94 (m, 3H), 6.12 (d, 1H), 4.02 (m, 1H), 3.89 (m, 2H), 3.63 (m, 4H), 3.42 (m, 4H), 3.17 (m, 2H), 2.93 (m, 2H), 2.79 (m, 2H), 2.46 (m, 4H), 2.10 (m, 2H), 1.82 (m, 2H), 1.57 (m; 4H), 1.23 (m, 12H).

EXAMPLE 859948

[0514] This example was made by substituting 4,4-difluoropiperidine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H),7.55 (m, 4H), 7.40 (d, 2H), 7.39 (m, 1H), 7.24 (m, 3H), 7.13 (m, 3H), 6.93 (d, 2H), 4.20 (m, 2H), 3.86 (m, 4H),3.42 (m, 4H), 3.17 (m, 8H), 2.28 (m, 4H), 2.18 (m, 4H).

EXAMPLE 855996

[0515] This example was made by substituting 2-methylpyrrolidine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.42 (s, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H),7.53 (m, 4H), 7.39 (d, 2H), 7.36 (m, 1H), 7.23 (m, 3H), 7.14 (m, 3H), 6.94 (d, 2H), 4.05 (m, 6H), 3.57 (m, 2H), 3.40 (m, 4H), 3.06 (m, 4H), 2.14 (m, 2H), 1.93 (m, 2H), 1.57 (m, 2H), 1.27 (m, 3H).

EXAMPLE 123A

[0516] 2.5 g/100 mL Rieke magnesium in diethyl ether (12.75 mL) at 25°C was treated with 1-bromo-3-methyl-2-butene (1.81 g), stirred for 1 hour, added to 2-methylpropane-2-sulfonic acid (2-benzyloxyethylidene)amide, prepared as described in J. Org. Chem. 2001, 26, 8772-8778, (1.85 g) in toluene (30 mL) at -78°C, and treated, at 25°C, with saturated NH_4Cl, ethyl acetate, and water. The extract was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10-20% acetone/hexanes.

EXAMPLE 123B

[0517] EXAMPLE 123A (1.01 g) in methanol (20 mL) at 25°C was treated with 4M HCl in dioxane (8 mL), stirred for 10 minutes, treated with 10% Pd/C, stirred under H_2 (balloon) for 18 hours, filtered through diatomaceous earth (Celite®), and concentrated. The concentrate was mixed with 1:1 2M Na_2CO_3/chloroform (60 mL), treated with benzylchloroformate (0.58 mL) and benzyltriethylammonium chloride (catalytic), and stirred 3 hours. The extract was washed with water, dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 3:1-2:1 hexanes/ethyl acetate.

EXAMPLE 123C

[0518] A mixture of EXAMPLE 123B (0.52 g), diphenyldisulfide (0.40 g), and tributylphosphine (0.81 g) in toluene (15 mL) at 85 °C was stirred for 18 hours, cooled to 25°C, and concentrated. The concentrate was flash chromatographed on silica gel with 20:1 then 10:1 and 5:1 hexanes/ethyl acetate.

EXAMPLE 123D

[0519] EXAMPLE 123C (0.52 g) in 30% HBr in acetic acid (15 mL) at 25°C was stirred for 2 hours, poured into 5% HCl (75 mL), washed with ethyl acetate, brought to pH 12 with 15% NaOH, and extracted with chloroform. The extract was dried ($MgSO_4$) and concentrated.

EXAMPLE 123E

[0520] This example was made by substituting EXAMPLE 123D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 123F

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-methyl-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide

[0521] This example was made by substituting EXAMPLE 123 E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.61 (s, 1H), 8.49 (d, 1H), 8.35 (d, 1H), 7.64-7.96 (m, 4H), 7.41-7.60 (m, 5H), 7.24-7.40 (m, 4H), 7.01-7.20 (m, 4H), 6.92 (d, 2H), 4.38 (m, 2H), 4.05 (m, 1H), 3.68-3.95 (m, 2H), 3.21-3.65 (m, 1H), 2.96-3.25 (m, 2H), 2.61-2.95 (m, 2H), 1.17-1.50 (m, 1H), 0.93 (d, 6H), 0.80 (t, 4H).

EXAMPLE 124

tert-butyl(5R)-5-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-6-(phenylsulfanyl)hexylcarbamate

[0522] This example was made by substituting tert-butyl (5R)-5-((4-(aminosulfonyl)-2-nitrophenyl)amino)-6-(phenylsulfanyl)hexylcarbamate, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.51 (d, 1H), 8.28 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.49-7.56 (m, 3H), 7.44-7.49 (m, 2H), 7.34-7.41 (m, 2H), 7.20-7.28 (m, 3H), 7.03-7.19 (m, 4H), 6.89 (d, 2H), 6.66-6.77 (m, 1H), 3.95-4.12 (m, 1H), 3.41 (m, 1H), 3.17-3.27 (m, 4H), 2.79-2.96 (m, 4H), 2.33-2.45 (m, 5H), 1.73 (m, 4H), 1.18-1.43 (m, 9H).

EXAMPLE 125

4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0523] EXAMPLE 124 (0.40 g) in dichloromethane (10 mL) was treated with 4M HCl in dioxane (2 mL), stirred for 20 hours at 25°C, and concentrated to give the desired product as the hydrochloride salt. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (s, 1H), 9.76 (s, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 7.85 (dd, 1H), 7.77 (d, 3H), 7.62 (m, 4H), 7.52 (d, 2H), 7.40 (d, 1H), 7.34 (d, 2H), 7.18-7.26 (m, 3H), 7.03-7.18 (m, 2H), 6.93 (d, 2H), 4.33 (m, 2H), 4.08 (m, 3H), 3.28-3.42 (m, 4H), 3.11 (m, 4H), 2.81-2.96 (m, 1H), 2.64-2.81 (m, 4H), 1.66-1.85 (m, 2H), 1.43-1.58 (m, 2H), 1.24-1.43 (m, 2H).

EXAMPLE 126

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-5-((methylsulfonyl)amino)-1-((phenylsulfanyl)methyl)pentyl)amino)-3-nitrobenzenesulfonamide

[0524] EXAMPLE 125 (0.075 g) in dichloromethane (7 mL) was treated with DIEA (0.055 g), cooled to 0°C, treated with methanesulfonylchloride (0.013 g), stirred for 1 hour, and treated with water. The extract was washed with water and brine, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-2.5% methanol in dichloromethane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (s, 1H), 8.52 (d, 1H), 8.30 (d, 1H), 7.84 (dd, 1H), 7.74 (d, 2H), 7.43-7.57 (m, 1H), 7.47 (s, 2H), 7.32-7.42 (m, 2H), 7.20-7.29 (m, 3H), 7.04-7.19 (m, 4H), 6.84-6.94 (m, 3H), 3.98-4.16 (m, 1H), 3.16-3.48 (m, 7H), 2.85-2.95 (m, 2H), 2.83 (s, 3H), 2.41 (m, 3H), 1.67-1.83 (m, 2H), 1.28-1.50 (m, 4H).

EXAMPLE 127

4-(((1R)-5-((aminocarbonyl)amino)-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide 127

[0525] EXAMPLE 125 (0.065 g) in dichloromethane (7 mL) at 25°C was treated with DIEA (0.048 g), cooled to 0°C, treated with trimethylsilylisocyanate (0.011 g), stirred at 25°C for 24 hours, treated with methanol (0.5 mL), and concen-

trated. The concentrate was purified by reverse phase HPLC (C-18) with 10-100% acetonitrile/water containing 0.1 % TFA. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (s, 1H), 9.56 (s, 1H), 8.52 (s, 1H), 8.31 (d, 1H), 7.84 (dd, 1H), 7.77 (d, 3H), 7.52 (m, 3H), 7.28-7.44 (m, 3H), 7.03-7.27 (m, 6H), 6.93 (d, 2H), 5.80-5.93 (m, 1H), 5.18-5.42 (m, 2H), 4.26-4.51 (m, 2H), 4.08 (m, 2H), 3.75-3.98 (m, 2H), 2.99-3.20 (m, 3H), 2.79-2.98 (m, 4H), 1.63-1.89 (m, 2H), 1.24-1.44 (m, 4H).

EXAMPLE 128A

[0526] A mixture of ethyl 4-fluorobenzoate (7.71 g), 1-(tert-butoxycarbonyl)piperazine (9.31 g), potassium carbonate (13.8 g), and 1-methyl-2-pyrrolidinone (20 mL) at 130°C was stirred for 16 hours, poured into water, and filtered. The filtrant was washed with water and dried in a vacuum oven at 50°C and 18 mmHg.

EXAMPLE 128B

[0527] This example was prepared by substituting EXAMPLE 128A for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 128C

[0528] This example was prepared by substituting EXAMPLE 128B for EXAMPLE 1C in EXAMPLE 1D.

EXAMPLE 128D

[0529] EXAMPLE 128C (3.7 g) in dichloromethane (10 mL) and 4M HCl in dioxane (10 mL) at 25°C was stirred for 5 hours, concentrated, treated with diethyl ether (20 mL), and filtered. The filtrant was washed with diethyl ether and dried in a vacuum oven at 50°C and 18 mm Hg.

EXAMPLE 128E

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(methylsulfanyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0530] EXAMPLE 128D (110 mg) in dichloromethane (2 mL) at 25°C was treated with 2-(methylsulfanyl)benzaldehyde (27 mg), N,N-DIEA (52 mg), and sodium triacetoxyborohydride (38 mg), stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 10% methanol/dichloromethane. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.36 (d, 1H), 7.78 (dd, 1H), 7.73 (d, 2H), 7.38-7.21 (m, 6H), 7.18 (d, 1H), 7.18-7.10 (m, 2H), 6.87 (d, 1H), 6.80 (d, 2H), 4.10-4.01 (m, 1H), 3.52 (s, 2H), 3.33 (d, 2H), 3.18 (t, 4H), 2.65-2.40 (m, 6H), 2.44 (s, 3H), 2.27 (s, 6H), 2.07-1.82 (m, 2H).

EXAMPLE 129A

[0531] 2-(methylsulfanyl)benzaldehyde (1 g) in dichloromethane (35 mL) was treated with 70% 3-chloroperoxybenzoic acid (3.32 g), stirred for 75 minutes, and concentrated. The concentrate was flash chromatographed on silica gel with 1:1 ethyl acetate/hexanes.

EXAMPLE 129B

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(methylsulfonyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0532] EXAMPLE 128D (110 mg) in dichloromethane (2 mL) was treated with EXAMPLE 129A (33 mg), 3.45 mmol/g N,N-DIEA resin (116 mg), and sodium triacetoxyborohydride (38 mg), stirred at 25°C for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 10% methanol/dichloromethane. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.21 (d, 1H), 7.98 (d, 1H), 7.81 (dd, 1H), 7.73 (d, 2H), 7.70 (td, 1H), 7.61 (d, 2H), 7.32 (dd, 2H), 7.24 (tt, 2H), 7.17 (tt, 1H), 6.90 (d, 1H), 6.82 (d, 2H), 4.11-4.01 (m, 1H), 3.93 (s, 2H), 3.42 (s, 3H), 3.33 (d, 2H), 3.18 (t, 4H), 3.00-2.80 (m, 2H), 2.62-2.48 (m, 4H), 2.56 (s, 6H), 2.13-1.98 (m, 2H).

EXAMPLE 130A

[0533] N-(tertbutoxycarbonyl)glycine methyl ester (5 g) in THF (60 mL) at 0°C was treated with 1.4M methylmagnesium

bromide in 3:1 toluene/THF (75.5 mL), stirred at 25°C for 16 hours, cooled to 0°C, treated with saturated NH_4Cl, and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 130B

[0534] EXAMPLE 130A (1 g) in THF (27 mL) at 0°C was treated with potassium tert-butoxide (663 mg), stirred for 30 minutes, and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/ethyl acetate.

EXAMPLE 130C

[0535] A mixture of EXAMPLE 130B (120 mg), 2-bromobenzaldehyde (289 mg), and sodium tert-butoxide (150 mg) in toluene (5 mL) in a sealable container was degassed/flushed with nitrogen three times and treated with dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium (II)·dichloromethane (82 mg). The container was sealed, and the mixture was heated at 120°C for 16 hours and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 130D

[0536] EXAMPLE 128C (4.02 g) in dioxane (7 mL) at 25°C was treated with 4M HCl (7 mL), stirred for 16 hours, neutralized and extracted with dichloromethane. The extract was concentrated. The concentrate was chromatographed on C_{18} with 1:1 acetonitrile/0.1% aqueous TFA.

EXAMPLE 130E

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(5,5-dimethyl-2-oxo-1,3-oxazolidin-3-yl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0537] EXAMPLE 130C (50 mg) in dichloromethane (2 mL) and methanol (0.4 mL) at 25°C was treated with EXAMPLE 130D (130 mg) and 2.38 mmol/g MP-BH_3CN (118 mg), stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 20% methanol/dichloromethane. ^1H NMR (300MHz, DMSO-d_6) δ 8.42 (d, 1H), 8.26 (d, 1H), 7.79 (dd, 1H), 7.74 (dd, 2H), 7.62-7.44 (m, 2H), 7.40-7.35 (m, 2H), 7.32 (d, 2H), 7.25 (td, 2H), 7.17 (tt, 1H), 6.88 (d, 1H), 6.82 (t, 2H), 4.10-4.01 (m, 1H), 3.78 (s, 2H), 3.49 (s, 2H), 3.34 (d, 2H), 3.23-3.14 (m, 6H), 2.90-2.62 (m, 4H), 2.43 (s, 6H), 2.10-1.90 (m, 2H), 1.50 (s, 6H).

EXAMPLE 131A

[0538] A mixture of 2-bromobenzaldehyde (4 g), butylamine (1.58 g), and 4A sieves (3 g) in dichloromethane (75 mL) at 25°C was stirred for 72 hours, filtered and concentrated.

EXAMPLE 131B

[0539] EXAMPLE 131A (400 mg) in THF (5 mL) at 0°C was treated with $MnCl_2$ (21 mg) and 2M cyclohexylmagnesium chloride in THF (1.67 mL), stirred for 25 minutes, treated with saturated NH_4Cl, and extracted with diethyl ether. The extract was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5% ethyl acetate/hexanes. Relevant fractions were combined and concentrated. The concentrate in 1:1 1,4-dioxane/water was stirred at 25°C for 16 hours and extracted with diethyl ether. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 131C

N-(4-(4-(2-cyclohexylbenzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0540] This example was prepared by substituting EXAMPLE 131B for EXAMPLE 130C in EXAMPLE 130D. ^1H NMR (300MHz, DMSO-d_6) δ 8.43 (d, 1H), 8.18 (d, 1H), 7.82 (dd, 1H), 7.73 (d, 2H), 7.45-7.37 (m, 1H), 7.30 (d, 2H), 7.28-7.07 (m, 6H), 6.92 (d, 1H), 6.82 (d, 2H), 4.12-4.01 (m, 1H), 3.51 (s, 2H), 3.33 (d, 2H), 3.17 (s, 4H), 3.05-2.88 (m, 3H), 2.70-2.52 (m, 2H), 2.61 (s, 6H), 2.16-1.98 (m, 2H), 1.84-1.65 (m, 6H), 1.50-1.22 (m, 6H).

EXAMPLE 132

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(morpholin-4-yl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0541] This example was prepared by substituting 2-morpholinobenzaldehyde for EXAMPLE 130C in EXAMPLE 130D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.22 (d, 1H), 7.81 (dd, 1H), 7.72 (d, 2H), 7.39 (dd, 1H), 7.32 (d, 2H), 7.28-7.22 (m, 3H), 7.20-7.04 (m, 3H), 6.90 (d, 1H), 6.81 (d, 2H), 4.14-4.00 (m, 1H), 3.75 (t, 4H), 3.57 (s, 2H), 3.33 (d, 2H), 3.18 (s, 4H), 2.94 (t, 4H), 2.88-2.50 (m, 6H), 2.56 (s, 6H), 2.15-1.90 (m, 2H).

EXAMPLE 133A

[0542] 2-propanethiol (797 mg) in 1-methyl-2-pyrrolidinone (20 mL) at 25°C was treated with 60% sodium hydride (419 mg) and 2-fluorobenzaldhyde (1 g), stirred for 10 minutes, treated with 1M NaOH (20 mL), and extracted with diethyl ether. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 133B

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(isopropylsulfanyl)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0543] This example was prepared by substituting EXAMPLE 133A for EXAMPLE 130C in EXAMPLE 130D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.30 (d, 1H), 7.78 (dd, 1H), 7.74 (d, 2H), 7.44 (dt, 2H), 7.33 (d, 2H), 7.28-7.22 (m, 4H), 7.17 (tt, 1H), 6.87 (d, 1H), 6.81 (d, 2H), 4.11-4.00 (m, 1H), 3.61 (s, 2H), 3.33 (d, 2H), 3.17 (t, 4H), 2.80-2.50 (m, 6H), 2.44-2.36 (m, 1H), 2.39 (s, 6H), 2.10-1.86 (m, 2H), 1.23 (d, 6H).

EXAMPLE 134A

[0544] A mixture of 3-(R)-((carbobenzyloxy)amino)-γ-butyrolactone, prepared according to the procedure described in J. Am. Chem. Soc. 1986, 108, 4943-4952, (15 g) and N-methylisopropylamine (25 mL) in diglyme (200 mL) at 120°C was stirred for 48 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/ethyl acetate.

EXAMPLE 134B

[0545] This example was prepared by substituting EXAMPLE 134A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 134C

[0546] This example was prepared by substituting EXAMPLE 134B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 134D

[0547] This example was prepared by substituting EXAMPLE 134C for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 134E

[0548] This example was prepared by substituting EXAMPLE 134D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 134F

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0549] This example was prepared by substituting EXAMPLE 8550516E and EXAMPLE 837538C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, and EXAMPLE 1C, respectively, in EXAMPLE 1D.
^{1}H NMR (300MHz, DMSO-d_6) δ 8.43 (d, 1H), 8.16 (s, 1H), 7.79 (d, 1H), 7.70 (d, 2H), 7.39-7.28 (m, 4H), 7.25 (td, 2H),

7.18 (dt, 1H), 7.12 (dt, 2H), 6.90 (d, 1H), 6.76 (d, 2H), 4.13-4.01 (m, 1H), 3.34 (d, 2H), 3.12 (s, 4H), 2.76 (s, 2H), 2.67-2.49 (m, 2H), 2.27 (s, 4H), 2.23-2.00 (m, 8H), 1.66 (s, 4H), 1.22-0.96 (m, 8H).

EXAMPLE 135A

[0550] This example was prepared by substituting di-n-propylamine for N-methylisopropylamine in EXAMPLE 134A.

EXAMPLE 135B

[0551] This example was prepared by substituting EXAMPLE 135A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 135C

[0552] This example was prepared by substituting EXAMPLE 135B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 135D

[0553] This example was prepared by substituting EXAMPLE 135C for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 135E

[0554] This example was prepared by substituting EXAMPLE 135D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 135F

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0555] This example was prepared by substituting EXAMPLE 135E and EXAMPLE 837538C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, and EXAMPLE 1C, respectively, in EXAMPLE 1D.
^{1}H NMR (300MHz, DMSO-d_6) δ 8.44 (d, 1H), 8.18 (s, 1H), 7.78 (d, 1H), 7.71 (d, 2H), 7.38-7.29 (m, 4H), 7.24 (tt, 2H), 7.18 (dt, 1H), 7.12 (d, 2H), 6.93-6.84 (m, 1H), 6.77 (d, 2H), 4.12-3.98 (m, 1H), 3.32 (d, 2H), 3.12 (s, 4H), 2.76 (s, 2H), 2.50-2.30 (m, 2H), 2.27 (s, 4H), 2.23-2.14 (m, 6H), 2.10-1.94 (m, 2H), 1.66 (s, 4H), 1.60-1.20 (m, 6H), 0.80 (s, 6H).

EXAMPLE 136

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dipropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0556] This example was prepared by substituting EXAMPLE 135E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.18 (s, 1H), 7.89 (d, 1H), 7.72 (d, 2H), 7.51 (dd, 1H), 7.48 (s, 4H), 7.40-7.34 (m, 2H), 7.32 (dd, 2H), 7.27-7.21, (m, 3H), 7.16 (tt, 1H), 6.94-6.85 (m, 1H), 6.79 (d, 2H), 4.12-4.00 (m, 1H), 3.38 (s, 2H), 3.33 (d, 2H), 3.13 (t, 4H), 3.00-2.85 (m, 2H), 2.40 (t, 4H), 2.08-1.93 (m, 2H), 1.60-1.20 (m, 8H), 0.81 (s, 6H).

EXAMPLE 137A

[0557] This example was prepared by substituting diethylamine for N-methylisopropylamine in EXAMPLE 134A.

EXAMPLE 137B

[0558] This example was prepared by substituting EXAMPLE 137A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 137C

[0559] This example was prepared by substituting EXAMPLE 137B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 137D

[0560] This example was prepared by substituting EXAMPLE 137C for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 137E

[0561] This example was prepared by substituting EXAMPLE 137D for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 137F

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0562] This example was prepared by substituting EXAMPLE 137E and EXAMPLE 837538C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, and EXAMPLE 1C, respectively, in EXAMPLE 1D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.44 (d, 1H), 8.18 (d, 1H), 7.81 (dd, 1H), 7.71 (d, 2H), 7.37 (d, 2H), 7.31 (dd, 2H), 7.24 (tt, 2H), 7.18 (dt, 1H), 7.12 (d, 2H), 6.92 (d, 1H), 6.77 (d, 2H), 4.17-4.04 (m, 1H), 3.34 (d, 2H), 3.12 (s, 4H), 2.95 (m, 6H), 2.76 (s, 2H), 2.27 (s, 4H), 2.19 (m, 4H), 2.06 (m, 2H), 1.66 (s, 4H), 1.08 (t, 6H).

EXAMPLE 138

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0563] This example was prepared by substituting EXAMPLE 137E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.18 (s, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.52 (dd, 1H), 7.48 (s, 4H), 7.40-7.35 (m, 2H), 7.31 (dd, 2H), 7.27-7.22, (m, 3H), 7.17 (tt, 1H), 6.94 (d, 1H), 6.79 (d, 2H), 4.15-4.04 (m, 1H), 3.38 (s, 2H), 3.35 (d, 2H), 3.14 (t, 4H), 3.13-2.95 (m, 6H), 2.40 (t, 4H), 2.15-2.00 (m, 2H), 1.10 (s, 6H).

EXAMPLE 139A

[0564] This example was made by substituting 3-bromobenzyl bromide for 2-bromobenzyl bromide in EXAMPLE 2A.

EXAMPLE 139B

[0565] This example was made by substituting EXAMPLE 139A and phenylboronic acid for EXAMPLE 2A and 4-chlorophenylboronic acid, respectively, in EXAMPLE 2B.

EXAMPLE 139C

[0566] This example was made by substituting EXAMPLE 139B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 139D

N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0567] This example was made by substituting EXAMPLE 139C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.12 (br, 1H), 9.92 (br, 1H), 8.78 (t, 1H), 8.60 (d, 1H), 7.91 (dd, 1H), 7.81 (m, 4H), 7.70 (m, 2H), 7.59 (t, 1H), 7.51 (m, 3H), 7.39 (m, 3H), 7.21 (m, 4H), 7.00 (d, 2H), 4.44 (m, 2H), 4.07 (m, 2H), 3.67 (t, 2H), 3.39 (m, 4H), 3.28 (t, 2H), 3.18 (m, 2H).

EXAMPLE 140

N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0568] This example was made by substituting EXAMPLE 139C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.15 (br, 1H), 10.11 (br, 1H), 9.46 (br, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 7.89 (d, 1H), 7.82 (m, 4H), 7.70 (m, 2H), 7.59 (t, 1H), 7.51 (m, 3H), 7.42 (m, 1H), 7.17 (m, 6H), 7.02 (d, 2H), 4.46 (m, 2H), 3.50 (m, 13H), 2.74 (d, 6H), 2.14 (q, 2H).

EXAMPLE 141

N-(4-(4-((1,1'-biphenyl)-3-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0569] This example was made by substituting EXAMPLE 139C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.17 (br, 1H), 10.10 (br, 1H), 9.77 (br, 1H), 8.55 (d, 1H), 8.31 (d, 1H), 7.89 (dd, 1H), 7.80 (m, 4H), 7.70 (m, 2H), 7.59 (t, 1H), 7.51 (m, 3H), 7.41 (m, 1H), 7.18 (m, 6H), 7.01 (d, 2H), 4.46 (m, 2H), 3.60 (m, 21H), 2.17 (q, 2H).

EXAMPLE 142A

[0570] 3,4-Difluorobenzoic acid (1 g) in THF (6 mL) and methanol (3 mL) at 25°C was treated with 2M (trimethylsilyl)diazomethane in hexane (4 mL), stirred for 2 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 5% ethyl acetate/hexane.

EXAMPLE 142B

[0571] EXAMPLE 142A in acetonitrile (6 mL) at 25°C was treated with K_2CO_3 (0.46 g) and piperazine (250 mg), refluxed for 24 hours, cooled to 25°C, treated with K_2CO_3 (0.40 g) and 2-phenylbenzyl bromide (0.53 mL), stirred for 18 hours, and concentrated. The concentate was partitioned between ethyl acetate and brine. The extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5% acetone/hexane.

EXAMPLE 142C

[0572] This example was made by substituting EXAMPLE 142B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 142D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0573] This example was made by substituting EXAMPLE 142C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.79 (br, 1H), 9.47 (br, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 7.86 (dd, 1H), 7.69 (m, 3H), 7.43 (m, 8H), 7.14 (m, 8H), 3.65 (m, 15H), 2.74 (d, 6H), 2.14 (q, 2H).

EXAMPLE 143

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0574] This example was made by substituting EXAMPLE 142C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.28 (br, 1H), 9.66 (m, 1H), 8.78 (t, 1H), 8.58 (d, 1H), 7.89 (dd, 1H), 7.74 (br, 1H), 7.68 (s, 1H), 7.64 (m, 1H), 7.48 (m, 4H), 7.37 (m, 5H), 7.23 (m, 4H), 7.05 (t, 2H), 4.38 (m, 2H), 3.24 (m, 12H).

EXAMPLE 144

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3-fluorobenzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0575] This example was made by substituting EXAMPLE 142C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.74 (br, 1H), 8.54 (d, 1H), 8.30 (d, 1H), 7.86 (dd, 1H), 7.68 (m, 3H), 7.48 (m, 9H), 7.13 (m, 6H), 3.63 (m, 23H), 2.18 (m, 2H).

EXAMPLE 145A

[0576] This example was made by substituting 3,4,5-trifluorobenzoic acid for 3,4-difluorobenzoic acid in EXAMPLE 142A.

EXAMPLE 145B

[0577] This example was made by substituting EXAMPLE 145A for EXAMPLE 142A in EXAMPLE 142B.

EXAMPLE 145C

[0578] This example was made by substituting EXAMPLE 145B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 145D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0579] This example was made by substituting EXAMPLE 145C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.72 (br, 1H), 9.44 (br, 1H), 8.51 (d, 1H), 8.27 (d, 1H), 7.84 (dd, 1H), 7.75 (m, 1H), 7.49 (m, 8H), 7.36 (m, 3H), 7.18 (m, 6H), 3.50 (m, 15H), 2.74 (d, 6H), 2.13 (q, 2H).

EXAMPLE 146

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0580] This example was made by substituting EXAMPLE 145C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.55 (br, 1H), 8.72 (t, 1H), 8.55 (d, 1H), 7.87 (dd, 1H), 7.73 (br, 1H), 7.34 (m, 16H), 4.36 (m, 2H), 3.25 (m, 12H).

EXAMPLE 147

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)-3,5-difluorobenzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0581] This example was made by substituting EXAMPLE 145C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.70 (br, 1H), 8.51 (d, 1H), 8.27 (d, 1H), 7.86 (dd, 1H), 7.75 (m, 1H), 7.49 (m, 7H), 7.35 (m, 3H), 7.25 (m, 2H), 7.16 (m, 4H), 4.40 (m, 2H), 4.16 (m, 2H), 3.38 (m, 19H), 2.15 (m, 2H).

EXAMPLE 148A

[0582] 1-Phenylimidazole (0.44 mL) in THF at 0°C was treated with 2.5M butyllithium in hexane (1.7 mL), stirred for 20 minutes, treated with DMF (0.8 mL), stirred for 1.5 hours, and treated with saturated aqueous NH_4Cl and ethyl acetate.

The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 15% acetone/hexane.

EXAMPLE 148B

[0583] A mixture of EXAMPLE 1A and EXAMPLE 148A in 1,2-dichloroethane (2 mL) at 25°C was treated with sodium triacetoxyborohydride (368 mg), stirred for 1 hour, and treated with dichloromethane and 1M NaOH. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 3-5% methanol/dichloromethane.

EXAMPLE 148C

[0584] This example was made by substituting EXAMPLE 148B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 148D

3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0585] This example was made by substituting EXAMPLE 148C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.02 (br, 1H), 8.78 (t, 1H), 8.59 (d, 1H), 7.90 (dd, 1H), 7.80 (d, 1H), 7.77 (d, 2H), 7.60 (m, 6H), 7.35 (m, 2H), 7.21 (m, 4H), 6.95 (d, 2H), 4.10 (m, 2H), 3.50 (m, 6H), 3.28 (t, 2H), 2.86 (m, 4H).

EXAMPLE 149

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-2-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0586] This example was made by substituting EXAMPLE 148C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.10 (br, 1H), 9.74 (br, 1H), 8.55 (d, 1H), 8.31 (d, 1H), 7.87 (dd, 1H), 7.83 (d, 1H), 7.78 (d, 2H), 7.61 (m, 6H), 7.17 (m, 6H), 6.95 (d, 2H), 3.53 (m, 23H), 2.19 (m, 2H).

EXAMPLE 150A

[0587] This example was made by substituting 1-phenylpyrazole for 1-phenylimidazole in EXAMPLE 148A.

EXAMPLE 150B

[0588] This example was made by substituting EXAMPLE 150A for EXAMPLE 148A in EXAMPLE 148B.

EXAMPLE 150C

[0589] This example was made by substituting EXAMPLE 150B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 150D

3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0590] This example was made by substituting EXAMPLE 150C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (300MHz, DMSO-d_6) δ 12.07 (br, 1H), 8.78 (t, 1H), 8.59 (d, 1H), 7.91 (dd, 1H), 7.76 (d, 2H), 7.75 (s, 1H), 7.52 (m, 5H), 7.36 (m, 2H), 7.21 (m, 4H), 6.95 (d, 2H), 6.67 (br, 1H), 3.28 (t, 2H), 3.22 (m, 12H).

EXAMPLE 151

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0591] This example was made by substituting EXAMPLE 150C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.10 (br, 1H), 9.76 (br, 1H), 8.55 (d, 1H), 8.31 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.74 (s, 1H), 7.54 (m, 5H), 7.17 (m, 6H), 6.95 (d, 2H), 6.64 (br, 1H), 3.25 (m, 23H), 2.17 (m, 2H).

EXAMPLE 152A

[0592] 3-Phenyl-3H-imidazole-4-carboxylic acid ethyl ester, prepared as described in Tet. Lett. 2000, 41, 5453-5456, (150 mg) in dichloromethane (2.5 mL) at -78 °C was treated with 1M DIBAL in dichloromethane (1.4 mL), stirred for 30 minutes, and treated with 25% aqueous potassium sodium tartrate, ethyl acetate (50 mL) and 25% aqueous potassium sodium tartrate (50 mL). The extract was washed with 25% aqueous potassium sodium tartrate (50 mL) and brine (50 mL) and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20-30-50% acetone/hexane.

EXAMPLE 152B

[0593] This example was made by substituting EXAMPLE 152A for EXAMPLE 148A in EXAMPLE 148B.

EXAMPLE 152C

[0594] This example was made by substituting EXAMPLE 152B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 152D

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-imidazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0595] This example was made by substituting EXAMPLE 152C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.36 (d, 1H), 7.88 (d, 1H), 7.80 (dd, 1H), 7.72 (d, 2H), 7.61 (m, 2H), 7.50 (m, 3H), 7.22 (m, 5H), 7.03 (m, 2H), 6.85 (d, 2H), 4.14 (m, 2H), 3.38 (m, 8H), 2.40 (m, 9H), 2.00 (m, 2H), 1.87 (m, 2H), 1.29 (m, 2H).

EXAMPLE 153A

[0596] A mixture of EXAMPLE 30C (50.5 mg) and 3-azetidinecarboxylic acid (13 mg) in methanol (1 mL) at 25°C were treated with sodium cyanoborohydride (8.5 mg), stirred for 4 hours, treated with silica gel and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane, 20% methanol/2% water/0.2% acetic acid/dichloromethane and 40% methanol/10% water/1% acetic acid/dichloromethane.

EXAMPLE 153B

[0597] A mixture of EXAMPLE 2C (1 g) and N-hydroxysuccinimide (296 mg) in ethyl acetate (9 mL) and THF (4 mL) at 25°C was treated with 1,3-dicyclohexylcarbodiimide (556 mg), stirred at 40°C for 6 hours and at 25°C for 16 hours, cooled to 0°C, treated with 40% ethyl acetate/hexane, and filtered through silica gel with 40% ethyl acetate/hexane. The filtrate was concentrated and the concentrate was flash chromatographed on silica gel with 35-40% ethyl acetate/hexane.

EXAMPLE 153C

1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-3-azetidinecarboxylic acid

[0598] A mixture of EXAMPLE 153A (28 mg) and EXAMPLE 153B (34 mg) in DMF (0.4 mL) at 25°C was treated with DBU (0.031 mL), stirred for 20 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane, 10% methanol/1% water/0.1% acetic acid/dichloromethane, and 20% methanol/20% water/2% acetic acid/dichloromethane. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.30 (br, 1H), 7.81 (dd, 1H), 7.72 (d, 2H), 7.46 (m, 5H), 7.26 (m, 7H), 6.93 (m, 1H), 6.81 (d, 2H), 4.06 (m, 2H), 2.99 (m, 16H), 1.65 (m, 4H).

EXAMPLE 154A

[0599] This example was made by substituting 1,1-dimethylethanolamine for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 154B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-hydroxy-2-methylpropyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0600] This example was made by substituting EXAMPLE 154A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.12 (d, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.51 (m, 5H), 7.26 (m, 7H), 6.93 (d, 1H), 6.78 (d, 2H), 4.10 (m, 2H), 3.26 (m, 7H), 2.92 (m, 2H), 2.75 (m, 2H), 2.40 (m, 4H), 2.08 (m, 2H), 1.14 (s, 6H).

EXAMPLE 155A

[0601] This example was made by substituting sarcosine for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 155B

(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)(methyl)amino)acetic acid

[0602] This example was made by substituting EXAMPLE 155A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.08 (br, 1H), 9.76 (br, 1H), 8.52 (d, 1H), 8.28 (d, 1H), 7.85 (dd, 1H), 7.77 (d, 2H), 7.69 (br, 1H), 7.43 (m, 7H), 7.15 (m, 6H), 6.93 (d, 2H), 5.56 (br, 1H), 4.21 (m, 2H), 4.03 (m, 2H), 3.37 (m, 11H), 2.79 (s, 3H), 2.19 (m, 2H), 1.65 (m, 2H).

EXAMPLE 156A

[0603] This example was made by substituting D-proline for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 156B

(2R)-1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-2-pyrrolidinecarboxylic acid

[0604] This example was made by substituting EXAMPLE 156A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.15 (br, 1H), 9.67 (br, 1H), 8.52 (d, 1H), 8.29 (d, 2H), 7.80 (m, 4H), 7.44 (m, 7H), 7.15 (m, 4H), 6.93 (d, 2H), 5.56 (br, 1H), 4.30 (m, 3H), 2.33 (m, 21H).

EXAMPLE 157A

[0605] This example was made by substituting isonipecotic acid for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 157B

1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-4-piperidinecarboxylic acid

[0606] This example was made by substituting EXAMPLE 157A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.05 (br, 1H), 8.47 (d, 1H), 8.21 (m, 1H), 7.81 (dd, 1H), 7.72 (d, 2H), 7.50 (m, 5H), 7.27 (m, 9H), 6.97 (m, 1H), 6.82 (d, 2H), 4.10 (m, 2H), 3.35 (m, 10H), 3.17 (m, 3H), 2.50 (m, 4H), 2.40 (m, 3H), 2.07 (m, 2H), 1.63 (m, 2H).

EXAMPLE 158A

[0607] This example was made by substituting 2-(methylamino)ethanol for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 158B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-hydroxyethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0608] This example was made by substituting EXAMPLE 158A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.18 (d, 1H), 7.81 (dd, 1H), 7.72 (d, 2H), 7.51 (m, 5H), 7.27 (m, 8H), 6.93 (d, 1H), 6.79 (d, 2H), 5.10 (m, 1H), 4.09 (m, 2H), 3.61 (m, 4H), 3.39 (m, 2H), 3.14 (m, 4H), 2.97 (m, 3H), 2.62 (m, 3H), 2.50 (m, 3H), 2.40 (m, 4H), 2.09 (m, 2H).

EXAMPLE 159A

[0609] This example was made by substituting L-proline for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 159B

(2S)-1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-2-pyrrolidinecarboxylic acid

[0610] This example was made by substituting EXAMPLE 159A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.10 (br, 1H), 9.67 (br, 1H), 8.52 (d, 1H), 8.29 (d, 2H), 7.46 (m, 15H), 6.93 (d, 2H), 5.56 (br, 1H), 4.24 (m, 3H), 2.35 (m, 21H).

EXAMPLE 160A

[0611] A mixture of 3-azetidinecarboxylic acid (251 mg) and 1M NaOH (6 mL) in dioxane (6 mL) at 25°C was treated with 95% benzyl chloroformate (0.54 mL), stirred for 18 hours and concentrated. The concentrate was treated with water, and the mixture was adjusted to pH greater than 10, washed with diethyl ether, adjusted to pH less than 3, and extracted with dichloromethane. The extract was dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 160B

[0612] EXAMPLE 833294A (574 mg) in dichloromethane (5 mL) at 0°C was treated with oxalyl chloride (0.75 mL) and DMF (2 drops), stirred for 1 hour, and concentrated twice from dichloromethane. The concentrate in ethyl acetate (5 mL) was treated with 30% aqueous ammonium hydroxide (1.3 mL) while cooling in a bath of cold water, stirred at 25°C for 2 hours, and treated with water and dichloromethane. The water layer was extracted with ethyl acetate, and the combined extracts were dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 160C

[0613] EXAMPLE 833294B (481 mg) in DMF (4 mL) at 25°C was treated with cyanuric chloride (189 mg), stirred for 30 minutes, and treated with water and ethyl acetate. The extract was washed with 1M $NaHCO_3$ and water and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% acetone/hexane.

EXAMPLE 160D

[0614] A mixture of EXAMPLE 160C (394 mg), azidotrimethylsilane (0.52 mL), and dibutyltin oxide (45 mg) in toluene (3.5 mL) at reflux was stirred for 38 hours, treated with methanol, and concentrated twice from methanol. The concentrate was treated with ethyl acetate and saturated $NaHCO_3$. The water layer was adjusted to pH less than 2 with 12M HCl and extracted with ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2% methanol/dichloromethane and 5% methanol/0.5% acetic acid/dichloromethane.

EXAMPLE 160E

[0615] A mixture of EXAMPLE 160D (224 mg) and palladium black (0.20 g) at 25°C was treated with a mixture of 96% formic acid (0.19 mL) in methanol (4 mL), stirred for 30 minutes, filtered, concentrated, and reconcentrated from methanol.

EXAMPLE 160F

[0616] This example was made by substituting EXAMPLE 160E for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 160G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(3-(2H-tetrazol-5-yl)azetidin-1-yl)propyl)amino)benzenesulfonamide

[0617] This example was made by substituting EXAMPLE 160F for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.48 (d, 1H), 8.36 (d, 1H), 7.82 (dd, 1H), 7.70 (m, 3H), 7.32 (m, 12H), 6.99 (d, 1H), 6.83 (d, 2H), 2.93 (m, 22H).

EXAMPLE 161A

[0618] A mixture of EXAMPLE 832729 (25 mg), Boc-Ala-Ala-OH (9 mg), EDAC·HCl (7 mg), and HoBT (6 mg) in dichloromethane (0.5 mL) at 25°C was treated with DIEA (0.009 mL), stirred for 16 hours, and treated with water and ethyl acetate. The extract was washed with 20% aqueous NH_4Cl and brine (25 mL) and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 8% methanol/dichloromethane.

EXAMPLE 161B

(2S)-2-amino-N-((1S)-2-(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)amino)-1-methyl-2-oxoethyl)propanamide

[0619] EXAMPLE 161A (15 mg) in dichloromethane (1 mL) at 25°C was treated with water (0.08 mL) and TFA (0.6 mL), stirred for 1 hour, and concentrated twice from dichloromethane. ^{1}H NMR (300MHz, DMSO-d_6) δ 12.09 (br, 1H), 9.68 (br, 1H), 8.52 (d, 1H), 8.51 (d, 1H), 8.29 (d, 1H), 8.05 (m, 3H), 7.77 (m, 4H), 7.52 (m, 3H), 7.37 (m, 3H), 7.17 (m, 7H), 6.93 (d, 2H), 3.55 (m, 17H), 1.92 (m, 2H), 1.30 (d, 3H), 1.18 (d, 3H).

EXAMPLE 162A

[0620] This example was made by substituting 5-pyrrolidin-2-yltetrazole, prepared as described in J. Med. Chem. 1985, 28, 1067-1071, for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 162B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(2-(2H-tetrazol-5-yl)pyrrolidin-1-yl)propyl)amino)benzenesulfonamide

[0621] This example was made by substituting EXAMPLE 162A for EXAMPLE 153A in EXAMPLE 153C. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.27 (d, 1H), 7.85 (dd, 1H), 7.73 (d, 2H), 7.43 (m, 7H), 7.17 (m, 7H), 6.88 (d, 2H), 4.11 (m, 3H), 2.88 (m, 17H), 1.93 (m, 4H).

EXAMPLE 163A

[0622] This example was made by substituting isonipecotic acid for 3-azetidinecarboxylic acid in EXAMPLE 160A.

EXAMPLE 163B

[0623] This example was made by substituting EXAMPLE 163A and methanesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.

EXAMPLE 163C

[0624] This example was made by substituting EXAMPLE 163B for EXAMPLE 160D in EXAMPLE 160E.

EXAMPLE 163D

[0625] This example was made by substituting EXAMPLE 163C for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 163E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-(((methylsulfonyl)amino)carbonyl)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0626] This example was made by substituting EXAMPLE 163D for EXAMPLE 153A in EXAMPLE 153C. MS (ESI) m/e 974.1 (M+H).

EXAMPLE 164A

[0627] This example was made by substituting EXAMPLE 18C for 19C in EXAMPLE 19D.

EXAMPLE 164B

[0628] 4-Bromobenzenesulfonyl chloride (0.40 g) in dichloromethane (10 mL) at 0°C was treated with TEA (0.26 mL), bis(2,4-dimethoxybenzyl)amine, prepared as described in Synthesis, 1991, 703-708, (0.50 g) and DMAP, (35 mg), stirred at 25°C for 4.5 hours, and treated with water and ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% ethyl acetate/hexane.

EXAMPLE 164C

[0629] A mixture of EXAMPLE 164A (356 mg), EXAMPLE 164B (151 mg), sodium tert-butoxide (91 mg), tris(dibenzylideneacetone)dipalladium(0) (32 mg) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (42 mg) in toluene (3 mL) at reflux was stirred for 3.5 hours, and treated with ethyl acetate and brine. The extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2-4% methanol/dichloromethane.

EXAMPLE 164D

[0630] A mixture of EXAMPLE 164C (0.34 g) and triethylsilane (0.25 mL) in dichloromethane (5 mL) at 25°C was treated with TFA (0.5 mL), stirred for 1.25 hours, and concentrated twice from dichloromethane. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane and 5-10% methanol/NH_3 gas-saturated/dichloromethane.

EXAMPLE 164E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0631] This example was made by substituting EXAMPLE 164D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^1H NMR (300MHz, DMSO-d_6) δ 7.71 (d, 2H), 7.57 (d,

2H), 7.48 (m, 5H), 7.29 (m, 8H), 6.86 (d, 2H), 6.51 (br, 1H), 6.47 (d, 2H).

EXAMPLE 165A

[0632] EXAMPLE 163A (0.50 g) in dichloromethane (5 mL) at 0°C was treated with DMF (2 drops) and oxalyl chloride (0.58 mL), stirred for 10 minutes, stirred at 25°C for 30 minutes, and concentrated twice from dichloromethane. The concentrate in THF (5 mL) at 25°C was treated with 50% aqueous hydroxylamine (0.46 mL), stirred for 17 hours and concentrated. The concentrate in ethyl acetate was washed with 0.5M HCl, water, and brine, dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 165B

[0633] This example was made by substituting EXAMPLE 165A for EXAMPLE 160D in EXAMPLE 160E.

EXAMPLE 165C

[0634] This example was made by substituting EXAMPLE 165B for 3-azetidinecarboxylic acid in EXAMPLE 153A.

EXAMPLE 165D

1-((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)-N-hydroxy-4-piperidinecarboxamide

[0635] This example was made by substituting EXAMPLE 165C for EXAMPLE 153A in EXAMPLE 153C.

EXAMPLE 166A

[0636] This example was made by substituting 4-bromo-2-chlorobenzenesulfonyl chloride for 4-bromobenzenesulfonyl chloride in EXAMPLE 164B.

EXAMPLE 166B

[0637] This example was made by substituting EXAMPLE 166A for EXAMPLE 164B in EXAMPLE 164C.

EXAMPLE 166C

[0638] This example was made by substituting EXAMPLE 166B for EXAMPLE 164C in EXAMPLE 164D.

EXAMPLE 166D

2-chloro-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0639] This example was made by substituting EXAMPLE 166C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 7.74 (d, 2H), 7.65 (d, 1H), 7.50 (m, 5H), 7.30 (m, 9H), 6.83 (d, 2H), 6.47 (m, 1H), 6.39 (m, 2H), 3.59 (m, 1H), 3.39 (s, 2H), 3.17 (m, 4H), 3.08 (m, 2H), 2.73 (m, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.40 (m, 4H), 2.00 (m, 1H), 1.75 (m, 1H).

EXAMPLE 167A

[0640] This example was made by substituting 4-bromo-2,6-dichlorobenzenesulfonyl chloride for 4-bromobenzenesulfonyl chloride in EXAMPLE 164B.

EXAMPLE 167B

[0641] This example was made by substituting EXAMPLE 167A for EXAMPLE 164B in EXAMPLE 164C.

EXAMPLE 167C

[0642] This example was made by substituting EXAMPLE 167B for EXAMPLE 164C in EXAMPLE 164D.

EXAMPLE 167D

2,6-dichloro-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0643] This example was made by substituting EXAMPLE 167C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 7.73 (d, 2H), 7.51 (m, 5H), 7.30 (m, 9H), 6.81 (d, 2H), 6.48 (m, 1H), 6.43 (s, 2H), 3.55 (m, 1H), 3.39 (s, 2H), 3.17 (m, 4H), 3.07 (m, 2H), 2.87 (m, 2H), 2.51 (s, 3H), 2.49 (s, 3H), 2.41 (m, 4H), 2.02 (m, 1H), 1.75 (m, 1H).

EXAMPLE 168A

[0644] Tropane in 1,2-dichloroethane (8 mL) at 0°C was treated with 1-chloroethyl chloroformate (0.47 mL), stirred for 15 minutes, refluxed for 2 hours, and concentrated twice from dichloromethane. The concentrate in methanol (8 mL) was refluxed for 2 hours and concentrated twice from dichloromethane.

EXAMPLE 168B

[0645] This example was made by substituting EXAMPLE 168A for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 168C

4-(((1R)-3-((1R,5S)-8-azabicyclo[3.2.1]oct-8-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0646] This example was made by substituting EXAMPLE 168B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.87 (m, 1H), 8.44 (d, 1H), 8.09 (m, 1H), 7.82 (m, 1H), 7.71 (d, 2H), 7.50 (m, 5H), 7.27 (m, 8H), 6.92 (m, 1H), 6.78 (d, 2H), 4.07 (m, 1H), 3.90 (m, 2H), 3.38 (m, 3H), 3.12 (m, 4H), 2.97 (m, 2H), 2.41 (m, 4H), 2.09 (m, 4H), 1.83 (m, 4H), 1.61 (m, 4H), 1.48 (m, 1H).

EXAMPLE 169A

[0647] This example was made by substituting 7-aza-bicyclo[2.2.1]heptane hydrochloride, prepared as described in Org. Lett. 2001,3, 1371-1374, for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 169B

4-(((1R)-3-(7-azabicyclo[2.2.1]hept-7-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0648] This example was made by substituting EXAMPLE 169A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 9.20 (m, 1H), 8.44 (d, 1H), 8.13 (m, 1H), 7.82 (d, 1H), 7.71 (d, 2H), 7.51 (m, 5H), 7.27 (m, 8H), 6.92 (d, 1H), 6.78 (d, 2H), 4.12 (m, 3H), 3.38 (m, 3H), 3.13 (m, 4H), 2.97 (m, 2H), 2.40 (m, 4H), 2.09 (m, 3H), 1.85 (m, 4H), 1.58 (m, 4H).

EXAMPLE 170A

[0649] This example was made by substituting 1-bromo-2-nitrobenze for 1-fluoro-2-(trifluoromethyl)benzene in EXAMPLE 18D.

EXAMPLE 170B

[0650] This example was made by substituting EXAMPLE 170A for 4-bromobenzenesulfonyl chloride in EXAMPLE 164B.

EXAMPLE 170C

[0651] EXAMPLE 170B (150 mg) at 25°C was treated with a mixture of 95% sodium hydride (8 mg) and 2-(phenylsulfanyl)ethanol (0.042 mL) in DMF (1.5 mL), stirred for 6 hours and treated with ethyl acetate and brine. The water layer was extracted with ethyl acetate, and the extract was dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 25% acetone/hexane.

EXAMPLE 170D

[0652] This example was made by substituting EXAMPLE 170C for EXAMPLE 164C in EXAMPLE 164D.

EXAMPLE 170E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(2-(phenylsulfanyl)ethoxy)benzenesulfonamide

[0653] This example was made by substituting EXAMPLE 170D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.32 (d, 1H), 8.08 (dd, 1H), 7.73 (d, 2H), 7.35 (m, 14H), 6.85 (d, 2H), 4.41 (t, 2H), 3.46 (m, 2H), 3.39 (t, 2H), 3.23 (m, 4H), 2.44 (m, 4H).

EXAMPLE 171A

[0654] This example was made by substituting 4-bromo-3-trifluoromethylbenzenesulfonyl chloride for 4-bromobenzenesulfonyl chloride in EXAMPLE 164B.

EXAMPLE 171B

[0655] This example was made by substituting EXAMPLE 171A for EXAMPLE 170B in EXAMPLE 170C.

EXAMPLE 171C

[0656] This example was made by substituting EXAMPLE 171B for EXAMPLE 164C in EXAMPLE 164D.

EXAMPLE 171D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(2-(phenylsulfanyl)ethoxy)-3-(trifluoromethyl)benzenesulfonamide

[0657] This example was made by substituting EXAMPLE 171C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.05 (m, 2H), 7.71 (d, 2H), 7.50 (m, 5H), 7.30 (m, 9H), 6.84 (d, 2H), 4.36 (t, 2H), 3.41 (s, 2H), 3.38 (t, 2H), 3.20 (m, 4H), 2.41 (m, 4H).

EXAMPLE 172A

[0658] 2(S)-Hydroxymethyl-4(R)-(toluene-4-sulfonyloxy)pyrrolidine-1-carboxylic acid tert-butyl ester, prepared as described in J. Med. Chem. 1991,34, 2787-2797), (467 mg) in methanol (21 mL) at 25°C was treated with 95% sodium methoxide (74 mg) in ethanol (3.5 mL), refluxed for 9.5 hours, and concentrated. The concentrate in water and diethyl ether was washed with brine and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% acetone/hexane.

EXAMPLE 172B

[0659] EXAMPLE 172A (178 mg) was treated with 1M HCL in methanol (20 mL), stirred for 21 hours, concentrated, and reconcentrated from diethyl ether.

EXAMPLE 172C

[0660] This example was made by substituting EXAMPLE 172B for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 172D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0661] This example was made by substituting EXAMPLE 172C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.33 (m, 1H), 7.79 (dd, 1H), 7.71 (d, 2H), 7.50 (m, 5H), 7.27 (m, 9H), 6.92 (d, 1H), 6.80 (d, 2H), 4.43 (m, 1H), 4.09 (m, 1H), 3.85 (m, 1H), 3.54 (m, 1H), 3.39 (s, 2H), 3.33 (m, 2H), 3.15 (m, 5H), 2.94 (m, 2H), 2.40 (m, 5H), 1.94 (m, 4H), 1.72 (m, 1H).

EXAMPLE 173A

[0662] This example was made by substituting 2(R)-hydroxymethyl-4(S)-(toluene-4-sulfonyloxy)pyrrolidine-1-carboxylic acid tert-butyl ester, prepared as described in J. Med. Chem. 1991,34, 2787-2797, for 2(S)-hydroxymethyl-4(R)-(toluene-4-sulfonyloxy)pyrrolidine-1-carboxylic acid tert-butyl ester in EXAMPLE 172A.

EXAMPLE 173B

[0663] This example was made by substituting EXAMPLE 173A for EXAMPLE 172A in EXAMPLE 172B.

EXAMPLE 173C

[0664] This example was made by substituting EXAMPLE 173B for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 173D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0665] This example was made by substituting EXAMPLE 173C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.25 (m, 1H), 7.81 (dd, 1H), 7.71 (d, 2H), 7.51 (m, 5H), 7.27 (m, 9H), 6.94 (d, 1H), 6.80 (d, 2H), 4.46 (m, 1H), 4.14 (m, 1H), 3.87 (m, 1H), 3.56 (m, 1H), 3.39 (s, 2H), 3.33 (m, 2H), 3.16 (m, 5H), 2.95 (m, 2H), 2.40 (m, 5H), 1.95 (m, 4H), 1.76 (m, 1H).

EXAMPLE 174

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0666] This example was made by substituting EXAMPLE 837538C and EXAMPLE 172C for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.32 (m, 1H), 7.81 (dd, 1H), 7.71 (d, 2H), 7.24 (m, 10H), 6.94 (d, 1H), 6.79 (d, 2H), 4.45 (m, 1H), 4.11 (m, 1H), 3.87 (m, 1H), 3.56 (m, 1H), 3.32 (m, 4H), 3.15 (m, 5H), 2.97 (m, 2H), 2.78 (m, 4H), 2.22 (m, 6H), 1.96 (m, 4H), 1.66 (m, 4H).

EXAMPLE 175

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0667] This example was made by substituting EXAMPLE 837538C and EXAMPLE 173C for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.26 (m, 1H), 7.80 (dd, 1H), 7.71 (d, 2H), 7.24 (m, 10H), 6.94 (d, 1H), 6.79 (d, 2H), 4.45 (m, 1H), 4.13 (m, 1H), 3.86 (m, 1H), 3.57 (m, 1H), 3.32 (m, 4H), 3.15 (m, 5H), 2.94 (m, 2H), 2.78 (m, 4H), 2.22 (m, 6H), 1.95 (m, 4H), 1.66 (m, 4H).

EXAMPLE 176

4-(((1R)-3-(7-azabicyclo[2.2.1]hept-7-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0668] This example was made by substituting EXAMPLE 837538C and EXAMPLE 169A for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (300MHz, DMSO-d_6) δ 9.18 (br, 1H), 8.44 (d, 1H), 8.14 (m, 1H), 7.80 (d, 1H), 7.71 (d, 2H), 7.24 (m, 9H), 6.93 (d, 1H), 6.78 (d, 2H), 4.09 (m, 2H), 3.35 (m, 4H), 3.14 (m, 6H), 2.76 (br s, 4H), 2.22 (m, 7H), 2.04 (m, 2H), 1.84 (m, 4H), 1.66 (m, 6H).

EXAMPLE 177A

[0669] This example was made by substituting 2,5-(cis)-dimethylpyrrolidine toluenesulfonate, prepared as described in A. R. Katritzky et al. J. Org. Chem. 1999,64, 1979-1985) for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 177B

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0670] This example was made by substituting EXAMPLE 837538C and EXAMPLE 177A for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.57 (br, 1H), 8.45 (d, 1H), 8.15 (m, 1H), 7.81 (d, 1H), 7.71 (d, 2H), 7.24 (m, 9H), 6.96 (m, 1H), 6.78 (d, 2H), 4.11 (m, 1H), 3.49 (m, 1H), 3.31 (m, 2H), 3.13 (m, 8H), 2.77 (m, 4H), 2.17 (m, 7H), 1.62 (m 6H), 1.29 (m, 6H).

EXAMPLE 178A

[0671] A mixture of 2(5H)-furanone (1 mL) and N-(methoxymethyl)-N-(trimethylsilylmethyl)benzylamine (4.2 mL) in dichloromethane (30 mL) at 0°C was treated with TFA (0.10 mL), stirred for 2.5 hours, and treated with dichloromethane and saturated aqueous $NaHCO_3$. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 15% acetone/hexane.

EXAMPLE 178B

[0672] EXAMPLE 178A (2.76 g) in 1,2-dichloroethane (25 mL) at 25°C was treated with 95% benzyl chloroformate (3.8 mL), refluxed for 24 hours and concentrated. The concentrate was flash chromatographed on silica gel with 25% acetone/hexane.

EXAMPLE 178C

[0673] EXAMPLE 178B (2.26 g) in THF (40 mL) at -78°C was treated with 1M DIBAL in dichloromethane (20 mL) then methanol (40 mL), filtered at 25°C, and concentrated. The concentrate was flash chromatographed on silica gel with 30% acetone/hexane.

EXAMPLE 178D

[0674] A mixture of EXAMPLE 178C (1.282 g) and triethylsilane (1.17 mL) in dichloromethane (25 mL) at 0°C was treated with BF_3·diethyl etherate (0.68 mL), stirred at 25°C for 3 hours, and treated with ethyl acetate and saturated aqueous $NaHCO_3$. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 15% acetone/hexane.

EXAMPLE 178E

[0675] This example was made by substituting EXAMPLE 178D for EXAMPLE 160D in EXAMPLE 160E.

EXAMPLE 178F

[0676] This example was made by substituting EXAMPLE 178E for azetidine hydrochloride in EXAMPLE 30D.

EXAMPLE 178G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]hept-5-yl)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0677] This example was made by substituting EXAMPLE 837538C and EXAMPLE 178F for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (300MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.23 (m, 1H), 7.77 (d, 1H), 7.71 (d, 2H), 7.24 (m, 10H), 6.96 (d, 1H), 6.79 (d, 2H), 4.08 (m, 1H), 3.61 (m, 2H), 2.68 (m, 26H), 1.66 (m, 6H).

EXAMPLE 179A

[0678] Cyclohexanol (880 mg) in DMF (2 mL) a 25°C was treated with 60% oily NaH (400 mg) and DMF (3 mL), stirred for 1.5 hours, treated with 15-crown-5 (0.6 mL), 4-fluoro-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, (440 mg), and DMF (0.5 mL), stirred for 1.5 hours, and treated with water and ethyl acetate. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatagraphed on silica gel with hexanes/ethyl acetate (10-30%).

EXAMPLE 179B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexyloxy)-3-nitrobenzenesulfonamide

[0679] This example was made by substituting EXAMPLE 179A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.31 (d, 1H), 8.07 (dd, 1H), 7.72 (d, 2H), 7.55 (t, 2H), 7.40 (m, 7H), 7.23 (dd, 1H), 6.85 (d, 2H), 6.73 (m, 1H), 3.51 (s, 2H), 3.23 (s, 4H), 2.44 (s, 4H), 1.85 (m, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 1.46 (m, 1H), 1.28 (m, 3H).

EXAMPLE 180A

[0680] This example was made by substituting cyclohexylmethanol for cyclohexanol in EXAMPLE 179A.

EXAMPLE 180B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexylmethoxy)-3-nitrobenzenesulfonamide

[0681] This example was made by substituting EXAMPLE 779855A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.41 (d, 1H), 8.17 (dd, 1H), 7.77 (s, 1H), 7.74 (s, 2H), 7.58 (d, 1H), 7.53 (m, 2H), 7.46 (m, 3H), 7.37 (m, 3H), 6.93 (d, 2H), 4.31 (br s, 1H), 3.80 (br s, 4H), 3.19 (br s, 3H), 2.83 (br s, 2H), 1.74 (m, 6H), 1.23 (m, 3H), 1.07 (m, 2H).

EXAMPLE 181A

[0682] This example was made by substituting 2-cyclohexylethanol for cyclohexanol in EXAMPLE 179A.

EXAMPLE 181B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(2-cyclohexylethoxy)-3-nitrobenzenesulfonamide

[0683] This example was made by substituting EXAMPLE 181A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.41 (d, 1H), 8.17 (dd, 1H), 7.77 (s, 1H), 7.75 (s, 2H), 7.60 (d, 1H), 7.53 (m, 2H), 7.52 (t, 2H), 7.43 (t, 1H), 7.37 (m, 3H), 6.92 (d, 2H), 4.30 (t, 4H), 2.95 (br s, 4H), 1.71 (d, 2H), 1.65 (m, 8H), 1.46 (m, 1H), 1.18 (m, 4H), 0.94 (m, 2H).

EXAMPLE 182A

[0684] Ammonium formate (5.8 g) in water (2.9 mL) at 25°C was treated with tetrahydropyran-4-one (1 g) in methanol (26 mL), stirred for 5 minutes, treated with 10% Pd/C (1.2g), stirred for 18 hours, filtered through diatomaceous earth (Celite®), and concentrated. A mixture of the concentrate in ethanol (23 mL) was stirred at 0°C as 12M HCl (1.7mL) was added dropwise, stirred for 1 hour, and filtered.

EXAMPLE 182B

[0685] This example was made by substituting EXAMPLE 182A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 182C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(tetrahydro-2H-pyran-4-ylamino)benzenesulfonamide

[0686] This example was made by substituting EXAMPLE 780431B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.62 (d, 1H), 8.27 (d, 1H), 7.93 (dd, 1H), 7.49 (d, 2H), 7.46 (d, 2H), 7.42 (d, 1H), 7.36 (m, 4H), 6.90 (d, 2H), 4.22 (br s, 1H), 3.93 (m, 1H), 3.86 (d, 2H), 3.72 (br s, 2H), 3.46 (t, 3H), 2.91 (br s, 4H), 2.49 (s, 2H), 1.91 (d, 2H), 1.62 (m, 2H).

EXAMPLE 183A

[0687] This example was made by substituting 2-cyclohexylethylamine for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 183B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((2-cyclohexylethyl)amino)-3-nitrobenzenesulfonamide

[0688] This example was made by substituting EXAMPLE 183A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.20 (br s, 1H), 8.62 (d, 1H), 8.52 (t, 1H), 7.94 (dd, 1H), 7.75 (d, 3H), 7.52 (m, 2H), 7.47 (d, 1H), 7.42 (m, 1H), 7.37 (m, 3H), 7.21 (d, 1H), 6.92 (d, 2H), 4.28 (br s, 2H), 3.75 (br s, 4H), 3.44 (m, 2H), 3.17 (br s, 2H), 2.86 (br s, 2H), 1.73 (d, 2H), 1.65 (m, 2H), 1.52 (m, 2H), 1.36 (m, 1H), 1.18 (m, 4H), 0.95 (m, 2H).

EXAMPLE 184A

[0689] This example was made by substituting N-methylcyclohexylamine for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 184B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(cyclohexyl(methyl)amino)-3-nitrobenzenesulfonamide

[0690] This example was made by substituting EXAMPLE 184A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.26 (d, 1H), 7.89 (dd, 1H), 7.75 (d, 3H), 7.52 (m, 2H), 7.47 (d, 2H), 7.43 (m, 2H), 7.37 (m, 3H), 6.92 (d, 2H), 4.27 (br s, 2H), 3.81 (br s, 3H), 3.56 (t, 1H), 3.15 (br s, 3H), 2.84 (br s, 2H), 2.65 (s, 3H), 1.76 (t, 4H), 1.59 (m, 3H), 1.35 (m, 2H), 1.15 (m, 1H).

EXAMPLE 185A

[0691] This example was made by substituting 3,3-dimethylglutarimide for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 185B

[0692] This example was made by substituting EXAMPLE 185A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 185C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(4,4-dimethylpiperidin-1-yl)-3-nitrobenzenesulfonamide

[0693] This example was made by substituting EXAMPLE 185B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.29 (d, 1H), 7.93 (dd, 1H), 7.74 (d, 3H), 7.51 (m, 2H), 7.47 (t, 2H), 7.42 (m, 2H), 7.35 (m, 3H), 6.91 (d, 2H), 4.29 (s, 2H), 3.79 (br s, 4H), 3.15 (m, 6H), 2.90 (br s, 2H), 1.42 (m, 4H), 0.96 (s, 6H).

EXAMPLE 186A

[0694] A mixture of tert-butyl-4-oxo-1-piperidinecarboxylate (2 g) in methanol (50 mL) 0°C was treated with $NaBH_4$ (2 g), stirred for 0.5 hours, stirred for 2 hours at 25°C, concentrated, treated with water, and extracted with dichloromethane. The extract was washed with water and dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 186B

[0695] This example was made by substituting EXAMPLE 186A for cyclohexanol in EXAMPLE 179A.

EXAMPLE 186C

tert-butyl 4-(4-(((4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitrophenoxy)-1-piperidinecarboxylate

[0696] This example was made by substituting EXAMPLE 186B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300MHz, DMSO-d_6) δ 8.26 (d, 1H), 8.03 (dd, 1H), 7.72 (d, 2H), 7.54 (m, 1H), 7.49 (m, 1H), 7.42 (m, 3H), 7.36 (m, 3H), 7.24 (m, 1H), 6.81 (d, 2H), 4.92 (m, 1H), 3.44 (m, 4H), 3.35 (m, 2H), 3.17 (d, 4H), 2.41 (m, 4H), 1.87 (m, 2H), 1.60 (m, 2H), 1.40 (s, 9H).

EXAMPLE 187

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(piperidin-4-yloxy)benzenesulfonamide

[0697] This example was made by substituting EXAMPLE 186C for EXAMPLE 21B in EXAMPLE 21C. ^{1}H NMR (400MHz, DMSO-d_6) δ 12.30 (br s, 1H), 11.58 (br s, 1H), 9.31 (s, 1H), 9.08 (s, 1H), 8.46 (d, 1H), 8.19 (dd, 1H), 8.18 (m, 1H), 7.76 (d, 2H), 7.71 (d, 1H), 7.52 (t, 2H), 7.46 (t, 2H), 7.42 (d, 1H), 7.35 (d, 3H), 6.92 (d, 2H), 5.11 (m, 1H), 4.35 (s, 2H), 3.84 (m, 2H), 3.67 (s, 3H), 3.38 (m, 2H), 3.12 (m, 2H), 2.73 (s, 2H), 2.72 (d, 1H); 2.15 (m, 2H), 1.98 (m, 2H).

EXAMPLE 188

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1-methylpiperidin-4-yl)oxy)-3-nitrobenzenesulfonamide

[0698] A mixture of EXAMPLE 187 (53 mg) and 37% formalin (6.6 μL), in 1:1 dichloromethane/methanol (1.5 mL) at 25°C was treated with 2.47mmol/g MP-$NaCNBH_3$ (55 mg) and DIEA (1 drop), stirred for 18 hours, treated with 1:1 dichloromethane/methanol (5 mL), and filtered through diatomaceous earth (Celite®). The filtrate was dried ($MgSO_4$), filtered, concentrated. The concentrate was flash chromatographed on silica gel with dichloromethane/2-5%methanol/0.5-1% NH_4OH. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.28 (d, 1H), 8.04 (dd, 1H), 7.72 (d, 2H), 7.54 (d, 1H), 7.45 (d, 2H), 7.46 (t, 2H), 7.42 (m, 3H), 7.36 (m, 3H), 7.24 (dd, 1H), 6.79 (d, 2H), 4.91 (s, 1H), 4.42 (s, 2H), 3.14 (m, 8H), 2.74 (s, 3H), 2.39 (m, 4H), 2.10 (s, 2H), 1.96 (s, 2H).

EXAMPLE 189

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide

[0699] This example was made by substituting 4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.
^{1}H NMR (400MHz, DMSO-d_6) δ 8.64 (m, 2H), 7.93 (dd, 1H), 7.78 (d, 2H), 7.72 (s, 1H), 7.52 (d, 4H), 7.40 (d, 2H), 7.33

(m, 1H), 7.24 (d, 1H), 6.92 (d, 2H), 4.22 (br s, 1H), 3.82 (br s, 2H), 3.29 (t, 4H), 2.88 (br s, 2H), 1.70 (m, 8H), 1.18 (m, 4H), 0.98 (m, 2H).

EXAMPLE 190A

[0700] Cyclohexanecarboxaldehyde (2 g) in methanol (20 mL) at 0°C was treated with n-propylamine (0.77 mL) and $NaCNBH_3$ (600 mg), stirred at 25°C for 18 hours, treated with water, and extracted with diethyl ether. The extract was dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 190B

[0701] This example was made by substituting EXAMPLE 190A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 190C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)(propyl)amino)-3-nitrobenzenesulfonamide

[0702] This example was made by substituting EXAMPLE 190B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, 1H), 7.89 (t, 1H), 7.76 (m, 2H), 7.70 (br s, 1H), 7.51 (m, 4H), 7.45 (d, 1H), 7.39 (m, 2H), 7.32 (m, 1H), 6.91 (d, 2H), 3.15 (dd, 2H), 3.07 (d, 2H), 2.05 (s, 2H), 1.61 (m, 6H), 1.48 (m, 3H), 1.11 (m, 4H), 0.78 (m, 5H).

EXAMPLE 191A

[0703] This example was made by substituting 1-N-Boc-4-cyanopiperidine for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 191B

[0704] A mixture of EXAMPLE 191A (520 mg), K_2CO_3 (1.7g), benzylbromide (0.62 mL), and acetone (7 mL) at reflux was stirred for 2.5 hours and concentrated. The concentrate was treated with water and 1M HCl, washed with hexanes, made basic with 2.5M NaOH, and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 191C

[0705] A mixture of EXAMPLE 191B (420 mg) and Raney nickel (4.5 g) in 20% NH_3/methanol (100 mL) at 25°C was stirred under H_2 at 60 psi for 16 hours, filtered, and concentrated.

EXAMPLE 191D

[0706] This example was made by substituting EXAMPLE 191C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 191E

4-(((1-benzylpiperidin-4-yl)methyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0707] This example was made by substituting EXAMPLE 191D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D.
^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 11.50 (br s, 1H), 10.68 (br s, 1H), 8.69 (m, 1H), 8.62 (s, 1H), 8.10 (br s, 1H), 7.91 (m, 1H), 7.74 (d, 3H), 7.57 (br s, 2H), 7.46 (m, 7H), 7.33 (m, 4H), 7.27 (d, 1H), 6.90 (d, 2H), 4.34 (br s, 2H), 4.20 (m, 2H), 3.81 (m, 2H), 3.26 (m, 7H), 3.15 (s, 2H), 2.79 (m, 5H), 2.49 (s, 1H), 1.87 (m, 4H), 1.60 (m, 2H), 1.24 (m, 1H), 0.85 (m, 1H).

EXAMPLE 192A

[0708] Cyclohexanemethylamine (2 mL) in THF (8 mL) at 25°C was treated with acetic formic anhydride, prepared as

described in Tet. Lett. 1982, 33, 3315, (5.7 g), stirred for 3.5 hours, concentrated, cooled to 0°C, treated with 1M borane THF (5.1 mL), stirred at reflux for 2.5 hours, concentrated, cooled to 0°C, treated with methanol (10 mL) and methanolic HCl (50 mL), stirred at reflux for 1 hour, concentrated, treated with water, and washed with diethyl ether. The water layer was made basic with 1M KOH and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 192B

[0709] This example was made by substituting EXAMPLE 192A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 192C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0710] This example was made by substituting EXAMPLE 192B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, 1H), 7.86 (dd, 1H), 7.74 (m, 3H), 7.52 (m, 2H), 7.47 (m, 2H), 7.42 (m, 2H), 7.35 (m, 3H), 6.91 (d, 2H), 4.29 (br s, 2H), 3.27 (d, 4H), 2.81 (m, 3H), 1.63 (m, 8H), 1.13 (m, 4H), 0.86 (m, 2H).

EXAMPLE 193A

[0711] This example was made by substituting 4-amino-1-benzylpiperidine for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 193B

4-((1-benzylpiperidin-4-yl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0712] This example was made by substituting EXAMPLE 193A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.95 (br s, 1H), 8.62 (br s, 1H), 8.15 (br s, 1H), 7.95 (d, 1H), 7.73 (d, 4H), 7.50 (m, 10H), 7.41 (m, 1H), 7.34 (m, 5H), 6.90 (d, 2H), 4.46 (br s, 1H), 4.34 (br s, 2H), 4.23 (br s, 1H), 3.92 (br s, 1H), 3.18 (m, 2H), 3.06 (m, 3H), 2.20 (m, 2H), 1.83 (br s, 1H).

EXAMPLE 194A

[0713] A mixture of tetrahydrothiopyran-4-one (1 g), hyroxylamine hydrochloride (1.5 g), and TEA (3 mL) in absolute ethanol (5 mL) was stirred at reflux for 3 hours, cooled to 25°C, treated with water, and extracted with dichloromethane. The extract was dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 194B

[0714] EXAMPLE 193A (300 mg) was treated with $LiAlH_4$ (400 mg) in THF (4 mL)/diethyl ether (11 mL), stirred at reflux for 5 hours, and processed as described in Fieser and Fieser, Reagents for Organic Synthesis, Vol 1, p.584.

EXAMPLE 194C

[0715] This example was made by substituting EXAMPLE 194B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 194D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(tetrahydro-2H-sulfanylpyran-4-ylamino)benzenesulfonamide

[0716] This example was made by substituting EXAMPLE 194C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 8.64 (d, 1H), 8.31 (d, 2H), 7.94 (dd, 1H), 7.74 (d, 3H), 7.47 (m, 4H), 7.34 (m, 3H), 6.91 (d, 4H), 4.29 (br s, 1H), 3.79 (m, 3H), 2.79 (m, 3H), 2.67 (m, 2H), 2.21 (m, 2H), 1.75 (m, 2H).

EXAMPLE 195A

[0717] This example was made by substituting ethyl 4-amino-1-piperidinecarboxylate for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 195B

ethyl 4-(4-(((4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-1-piperidinecarboxylate

[0718] This example was made by substituting EXAMPLE 195A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (br s, 1H), 8.64 (d, 1H), 8.29 (d, 1H), 7.95 (dd, 1H), 7.75 (d, 3H), 7.54 (m, 2H), 7.48 (m, 1H), 7.43 (m, 1H), 7.37 (m, 2H), 6.92 (d, 2H), 4.36 (br s, 2H), 4.05 (m, 2H), 3.94 (m, 3H), 3.77 (br s, 3H), 3.01 (br s, 4H), 2.83 (br s, 2H), 1.94 (d, 2H), 1.55 (m, 2H), 1.19 (t, 5H).

EXAMPLE 196A

[0719] This example was made by substituting 1-bromopropane for benzyl bromide in EXAMPLE 191B.

EXAMPLE 196B

[0720] This example was made by substituting EXAMPLE 196A for EXAMPLE 191B in EXAMPLE 797197C.

EXAMPLE 196C

[0721] This example was made by substituting EXAMPLE 196B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 196D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1-propylpiperidin-4-yl)methyl)amino)benzenesulfonamide

[0722] This example was made by substituting EXAMPLE 196C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, 1H), 8.43 (t, 2H), 7.90 (dd, 1H), 7.72 (d, 2H), 7.53 (m, 1H), 7.42 (m, 4H), 7.35 (m, 3H), 7.24 (m, 1H), 7.10 (d, 1H), 6.78 (d, 2H), 3.41 (s, 2H), 3.36 (m, 5H), 3.13 (m, 4H), 2.77 (m, 3H), 2.39 (m, 4H), 1.87 (d, 3H), 1.59 (m, 2H), 1.42 (m, 2H), 0.87 (t, 3H).

EXAMPLE 197A

[0723] This example was made by substituting isopropylamine for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 197B

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(isopropylamino)-3-nitrobenzenesulfonamide

[0724] This example was made by substituting EXAMPLE 197A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.64 (d, 1H), 8.24 (d, 1H), 7.95 (dd, 1H), 7.74 (m, 3H), 7.50 (m, 4H), 7.42 (m, 1H), 7.35 (m, 3H), 7.27 (d, 1H), 6.91 (d, 2H), 4.25 (br s, 2H), 4.00 (m, 1H), 1.28 (d, 6H).

EXAMPLE 198A

[0725] A mixture of tributylphosphine (0.8 mL), (1,1'-azodicarbonyl)dipiperidine (0.8 g), and THF (5.1 mL) at 25°C was stirred for 10 minutes, treated with tert-butyl N-(2-hydroxyethyl)carbamate (0.32 mL), 2-mercaptothiazole (500 mg), and THF (5 mL), stirred for 20 hours, treated with ethyl acetate (50 mL), washed with water, dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5-30% ethyl acetate/hexanes.

EXAMPLE 198B

[0726] This example was made by substituting EXAMPLE 198A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 198C

[0727] This example was made by substituting EXAMPLE 198B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 198D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)benzenesulfonamide

[0728] This example was made by substituting EXAMPLE 198C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (t, 1H), 8.61 (d, 1H), 7.96 (dd, 1H), 7.73 (m, 4H), 7.62 (d, 1H), 7.51 (m, 2H), 7.46 (d, 2H), 7.40 (m, 2H), 7.34 (m, 4H), 6.91 (d, 2H), 4.28 (br s, 2H), 3.81 (m, 4H), 3.50 (t, 4H), 2.06 (s, 2H).

EXAMPLE 199A

[0729] This example was made by substituting 4-phenyl-2-mercaptothiazole for 2-mercaptothiazole in EXAMPLE 198A.

EXAMPLE 199B

[0730] This example was made by substituting EXAMPLE 199A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 199C

[0731] This example was made by substituting EXAMPLE 199B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 199D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-((4-phenyl-1,3-thiazol-2-yl)sulfanyl)ethyl)amino)benzenesulfonamide

[0732] This example was made by substituting EXAMPLE 199C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (m, 1H), 8.57 (d, 1H), 8.00 (s, 1H), 7.91 (m, 3H), 7.73 (d, 2H), 7.54 (m, 1H), 7.39 (m, 11H), 7.24 (m, 1H), 6.86 (d, 2H), 3.87 (m, 2H), 3.57 (dd, 2H), 3.43 (s, 2H), 3.22 (m, 4H), 2.39 (m, 4H).

EXAMPLE 200A

[0733] This example was made by substituting 2-mercaptobenzthiazole for 2-mercaptothiazole in EXAMPLE 198A.

EXAMPLE 200B

[0734] This example was made by substituting EXAMPLE 200A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 200C

[0735] This example was made by substituting EXAMPLE 200B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 200D

4-((2-(1,3-benzothiazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0736] This example was made by substituting EXAMPLE 200C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.86 (t, 1H), 8.59 (d, 1H), 7.76 (m, 4H), 7.54 (m, 2H), 7.48 (m, 2H), 7.43 (m, 2H), 7.36 (m, 4H), 6.92 (d, 2H), 4.31 (br s, 2H), 3.91 (m, 2H), 3.66 (t, 4H), 2.97 (br s, 4H).

EXAMPLE 201

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)benzenesulfonamide

[0737] This example was made by substituting EXAMPLE 198C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (m, 1H), 8.61 (d, 1H), 7.95 (dd, 1H), 7.74 (m, 4H), 7.71 (d, 1H), 7.62 (d, 1H), 7.52 (m, 4H), 7.40 (m, 1H), 7.39 (m, 2H), 7.37 (m, 1H), 7.33 (m, 1H), 6.91 (d, 2H), 3.81 (m, 4H), 3.50 (m, 4H), 3.32 (m, 1H), 3.27 (m, 1H), 2.49 (m, 1H), 2.06 (s, 1H).

EXAMPLE 202A

[0738] This example was made by substituting 2-mercaptobenzoxazole for 2-mercaptothiazole in EXAMPLE 198A.

EXAMPLE 202B

[0739] This example was made by substituting EXAMPLE 202A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 202C

[0740] This example was made by substituting EXAMPLE 202B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 202D

4-((2-(1,3-benzoxazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0741] This example was made by substituting EXAMPLE 202C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (m, 1H), 8.58 (d, 1H), 8.00 (dd, 1H), 7.76 (d, 2H), 7.71 (br s, 1H), 7.57 (m, 2H), 7.50 (m, 4H), 7.39 (m, 2H), 7.29 (m, 3H), 6.91 (d, 2H), 4.22 (br s, 2H), 3.92 (m, 2H), 3.60 (t, 4H), 2.97 (m, 4H).

EXAMPLE 203

4-((2-(1,3-benzothiazol-2-ylsulfanyl)ethyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0742] This example was made by substituting EXAMPLE 200C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 8.85 (t, 1H), 8.58 (d, 1H), 8.01 (dd, 1H), 7.97 (d, 1H), 7.75 (m, 3H), 7.71 (br s, 1H), 7.51 (m, 4H), 7.37 (m, 4H), 6.91 (d, 2H), 4.26 (br s, 2H), 3.90 (m, 2H), 3.64 (t, 4H), 2.96 (m, 6H).

EXAMPLE 204A

[0743] This example was made by substituting 2-mercaptopyrimidine for 2-mercaptothiazole in EXAMPLE 198A.

EXAMPLE 204B

[0744] This example was made by substituting EXAMPLE 204A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 204C

[0745] This example was made by substituting EXAMPLE 204B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 204D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(pyrimidin-2-ylsulfanyl)ethyl)amino)benzenesulfonamide

[0746] This example was made by substituting EXAMPLE 204C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 8.83 (t, 1H), 8.66 (d, 2H), 8.63 (d, 1H), 8.04 (dd, 1H), 7.76 (d, 2H), 7.72 (br s, 1H), 7.52 (m, 5H), 7.40 (d, 2H), 7.33 (m, 1H), 7.24 (t, 1H), 6.92 (d, 2H), 4.29 (br s, 2H), 3.78 (m, 4H), 3.39 (t, 4H), 2.85 (br s, 2H).

EXAMPLE 205A

[0747] This example was made by substituting 2-bromoethylamine hydrochloride for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 205B

[0748] EXAMPLE 205A and 2-mercaptoimidazole were subjected to the procedure described in J.Med.Chem. 1995, 38, 1067.

EXAMPLE 205C

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((1-phenyl-1H-pyrazol-5-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0749] This example was made by substituting EXAMPLE 205B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (t, 1H), 8.63 (d, 1H), 7.94 (dd, 1H), 7.76 (d, 3H), 7.53 (m, 4H), 7.40 (d, 2H), 7.34 (m, 1H), 7.30 (m, 1H), 6.93 (d, 2H), 4.26 (br s, 2H), 3.72 (m, 4H), 3.42 (t, 4H), 2.98 (br s, 4H).

EXAMPLE 206

4-(((1-benzylpiperidin-4-yl)methyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0750] This example was made by substituting EXAMPLE 191D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 11.43 (br s, 1H), 10.67 (br s, 1H), 8.73 (t, 1H), 8.63 (d, 1H), 8.15 (m; 1H), 7.92 (dd, 1H), 7.76 (d, 2H), 7.59 (m, 2H), 7.53 (m, 4H), 7.44 (m, 4H), 7.38 (d, 2H), 7.33 (m, 1H), 7.28 (d, 1H), 6.93 (d, 2H), 4.34 (br s, 2H), 4.22 (d, 2H), 3.89 (d, 2H), 3.37 (m, 4H), 3.31 (d, 2H), 3.25 (d, 2H), 2.84 (m, 4H), 1.88 (d, 3H), 1.61 (m, 2H).

EXAMPLE 207

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((2-bromoethyl)amino)-3-nitrobenzenesulfonamide

[0751] This example was made by substituting EXAMPLE 205A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (br s, 1H), 8.75 (m, 1H), 8.65 (d, 1H), 7.96 (dd, 1H), 7.75 (d, 3H), 7.53 (m, 2H), 7.48 (m, 2H), 7.43 (m, 1H), 7.36 (m, 4H), 6.92 (d, 2H), 4.29 (br s, 2H), 3.88 (m, 4H), 3.82 (m, 2H), 3.72 (t, 2H), 3.03 (m, 4H).

EXAMPLE 208A

[0752] This example was made by substituting 4-methylthiazole-2-thiol for 2-mercaptoimidazole in EXAMPLE 205B.

EXAMPLE 208B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-((4-methyl-1,3-thiazol-2-yl)sulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0753] This example was made by substituting EXAMPLE 208A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (br s, 1H), 8.81 (t, 1H), 8.63 (d, 1H), 7.95 (dd, 1H), 7.76 (d, 2H), 7.73 (br s, 1H), 7.52 (m, 3H), 7.39 (d, 2H), 7.34 (m, 1H), 6.93 (d, 2H), 4.25 (br s, 2H), 3.82 (m, 2H), 3.48 (m, 4H), 3.02 (m, 4H), 2.29 (s, 3H), 2.07 (s, 2H).

EXAMPLE 209A

[0754] This example was made by substituting benzylamine for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and 4-methoxycyclohexane carboxylic acid for EXAMPLE 2C in EXAMPLE 2D.

EXAMPLE 209B

[0755] This example was made by subsituting EXAMPLE 209A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 209C

[0756] EXAMPLE 209B (710 mg) and $Pd(OH)_2$ (0.28g) in methanol (70 mL) at 50°C was stirred under H_2 (60 psi) for 22 hours, cooled to 25°, filtered, and concentrated.

EXAMPLE 209D

[0757] This example was made by substituting EXAMPLE 209C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 209E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((4-methoxycyclohexyl)methyl)amino)-3-nitrobenzenesulfonamide

[0758] This example was made by substituting EXAMPLE 209D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.48 (t, 1H), 7.90 (dd, 1H), 7.72 (d, 2H), 7.51 (m, 1H), 7.47 (s, 3H), 7.37 (m, 2H), 7.25 (m, 1H), 7.14 (d, 1H), 6.84 (d, 2H), 3.39 (s, 2H), 3.36 (m, 1H), 3.27 (m, 4H), 3.19 (m, 5H), 2.40 (t, 4H), 1.80 (m, 2H), 1.69 (m, 1H), 1.48 (m, 2H), 1.33 (m, 4H).

EXAMPLE 210A

[0759] This example was made by substituting 2-mercaptothiophene for 2-mercaptothiazole in EXAMPLE 198A.

EXAMPLE 210B

[0760] This example was made by substituting EXAMPLE 210A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 210C

[0761] This example was made by substituting EXAMPLE 210B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 210D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(2-thienylsulfanyl)ethyl)amino)benzenesulfonamide

[0762] This example was made by substituting EXAMPLE 210C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 (t, 1H), 8.62 (d, 1H), 7.90 (dd, 1H), 7.75 (m, 2H), 7.61 (dd, 1H), 7.54 (m, 2H), 7.49 (m, 2H), 7.43 (m, 1H), 7.36 (m, 2H), 7.21 (dd, 1H), 7.13 (d, 1H), 7.02 (dd, 1H), 6.92 (d, 2H), 4.36 (br s, 2H), 3.63 (m, 4H), 3.11 (t, 4H), 2.54 (s, 4H).

EXAMPLE 211A

[0763] A mixture of Boc-2-amino-2-methylpropanol (633 mg) and 2-thienyldisulfide (1 g) in THF (12 mL) at 25°C was treated with tributylphosphine (1.1 mL), heated at 85°C for 2.5 hours, treated with ethyl acetate, washed with water, dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatograped on silica gel with 30-70% ethyl acetate/hexanes.

EXAMPLE 211B

[0764] This example was made by substituting EXAMPLE 211A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 211C

[0765] This example was made by substituting EXAMPLE 8030757B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 211D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(2-thienylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0766] This example was made by substituting EXAMPLE 211C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, 1H), 8.54 (s, 1H), 7.82 (dd, 1H), 7.79 (d, 2H), 7.72 (br s, 1H), 7.52 (m, 4H), 7.33 (d, 2H), 7.21 (dd, 1H), 6.96 (dd, 1H), 6.94 (d, 2H), 6.66 (dd, 1H), 4.19 (br s, 4H), 2.90 (br s, 6H), 1.54 (s, 6H).

EXAMPLE 212A

[0767] This example was made by sustituting EXAMPLE 19A for Boc-2-amino-2-methylpropanol and EXAMPLE 22A for 2-thienyldisulfide in EXAMPLE 211A.

EXAMPLE 212B

[0768] This example was made by substituting EXAMPLE 212A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 212C

[0769] This example was made by substituting EXAMPLE 212B for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 212D

[0770] This example was made by substituting EXAMPLE 212C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 212E

[0771] This example was made by substituting EXAMPLE 212D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.97 (br s, 1H), 8.61 (d, 1H), 8.34 (d, 1H), 7.95 (dd, 1H), 7.75 (d, 2H), 7.72 (br s, 1H), 7.66 (d, 1H), 7.59 (d, 1H), 7.51 (d, 4H), 7.32 (m, 1H), 6.92 (d, 2H), 4.35 (m, 2H), 4.22 (br s, 2H), 3.95 (br s, 4H), 3.21 (m, 4H), 2.94 (m, 6H), 2.20 (m, 2H).

EXAMPLE 213A

[0772] This example was prepared by substituting 2-mercaptopyrimidine for 2-mercaptothiazole in EXAMPLE 22A.

EXAMPLE 213B

[0773] This example was made by sustituting EXAMPLE 18A for Boc-2-amino-2-methylpropanol and EXAMPLE 213A for 2-thienyldisulfide in EXAMPLE 211A.

EXAMPLE 213C

[0774] This example was made by substituting EXAMPLE 213B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 213D

[0775] This example was made by substituting EXAMPLE 213C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 213E

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(pyrimidin-2-ylsulfanyl)butanamide

[0776] This example was made by substituting EXAMPLE 212D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.08 (br s, 1H), 9.86 (br s, 1H), 8.97 (d, 1H) 8.62 (d, 2H,) 8.60 (d, 1H), 7.99 (dd, 1H), 7.77 (d, 2H), 7.74 (br s, 1H), 7.53 (m, 5H), 7.39 (d, 2H), 7.34 (m, 1H), 7.22 (t, 1H), 6.93 (d, 2H), 4.59 (m, 1H), 4.29 (br s, 2H), 3.42 (dd, 3H), 3.04 (dd, 2H), 2.95 (s, 4H), 2.81 (m, 5H).

EXAMPLE 214A

[0777] This example was made by sustituting EXAMPLE 19A for Boc-2-amino-2-methylpropanol in EXAMPLE 211A.

EXAMPLE 214B

[0778] This example was made by substituting EXAMPLE 214A for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 214C

[0779] This example was made by substituting EXAMPLE 214B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 214D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-3-oxo-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0780] This example was made by substituting EXAMPLE 214C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (br s, 1H), 8.77 (d, 1H), 7.86 (dd, 1H), 7.74 (d, 2H), 7.71 (br s, 1H), 7.55 (dd, 1H), 7.51 (m, 4H), 7.38 (d, 2H), 7.32 (m, 1H), 7.08 (d, 1H), 7.04 (dd, 1H), 6.94 (dd, 1H), 6.91 (d, 2H), 4.39 (m, 2H), 3.51 (m, 5H), 3.25 (m, 4H), 2.99 (dd, 2H), 2.75 (dd, 2H).

EXAMPLE 215A

[0781] This example was made by substituting EXAMPLE 213A for 2-thienyldisulfide in EXAMPLE 211A.

EXAMPLE 215B

[0782] This example was made by substituting EXAMPLE 215A for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 215C

[0783] This example was made by substituting EXAMPLE 215B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 215D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(pyrimidin-2-ylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0784] This example was made by substituting EXAMPLE 215C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.53 (d, 2H), 8.49 (br s, 1H), 7.97 (dd, 1H), 7.74 (d, 2H), 7.53 (m, 2H), 7.47 (br s, 4H), 7.37 (m, 2H), 7.25 (m, 1H), 7.11 (t, 1H), 6.87 (d, 2H), 3.80 (br s, 2H), 3.41 (br s, 3H), 3.22 (m, 5H), 2.40 (m, 4H), 1.58 (br s, 6H).

EXAMPLE 216C

[0785] This example was made by substituting EXAMPLE 22C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 216D

3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(1,3-thiazol-2-ylsulfanyl)butanamide

[0786] This example was made by substituting EXAMPLE 216C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.05 (br s, 1H), 8.91 (d, 1H), 8.59 (d, 1H), 7.92 (dd, 1H), 7.77 (d, 2H), 7.74 (br s, 1H), 7.71 (d, 1H), 7.60 (d, 1H), 7.52 (m, 4H), 7.42 (d, 1H), 7.39 (d, 2H), 7.34 (m, 1H), 6.93 (d, 2H), 4.63 (m, 1H), 4.30 (br s, 1H), 3.69 (m, 2H), 3.02 (m, 2H), 2.93 (br s, 4H), 2.82 (d, 1H), 2.79 (br s, 4H).

EXAMPLE 217A

[0787] This example was made by substituting EXAMPLE 214C for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 217B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0788] This example was made by substituting EXAMPLE 217A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.38 (m, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.58 (dd, 1H), 7.51 (dd, 1H), 7.47 (m, 4H), 7.37 (m, 2H), 7.24 (m, 1H), 7.10 (dd, 1H), 6.98 (m, 2H), 6.85 (d, 2H), 4.08 (m, 1H), 3.54 (br s, 4H), 3.40 (s, 2H), 3.19 (m, 6H), 2.39 (m, 10H), 2.00 (m, 1H), 1.83 (m, 1H).

EXAMPLE 218A

[0789] A mixture of EXAMPLE 18A (1.6 g) and 10%Pd/C (0.16 g) in methanol (70 mL) at 25°C was stirred under H_2 (60 psi) for 3 hours, filtered and concentrated.

EXAMPLE 218B

[0790] This example was made by substituting EXAMPLE 218A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 218C

[0791] Methanesulfonyl chloride (68 μL) was treated with EXAMPLE 218B (270 mg) and pyridine (1 mL) at 0°C, stirred for 1 hour, treated with 1M HCl (10 mL) and water, stirred for 0.5 hours, and filtered. The filtrant was washed with water and concentrated.

EXAMPLE 218D

[0792] A mixture of EXAMPLE 218C (120 mg), 4-(trifluoromethoxy)thiophenol (140 mg), K_2CO_3 (158 mg), and acetone (14 mL) at reflux was stirred for 30 minutes, cooled to 25°C, and concentrated. The concentrate in dichloromethane was washed with water and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 1-2% dichloromethane/methanol.

EXAMPLE 218E

[0793] This example was made by substituting EXAMPLE 218D for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 218F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0794] This example was made by substituting EXAMPLE 218D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (br s, 1H), 9.58 (br s, 1H), 8.54 (d, 1H), 8.26 (d, 1H), 7.89 (dd, 1H), 7.77 (d, 2H), 7.72 (br s, 1H), 7.52 (d, 4H), 7.40 (d, 2H), 7.33 (m, 3H), 7.24 (d, 1H), 7.12 (d, 2H), 6.92 (d, 2H), 4.23 (m, 2H), 3.43 (m, 4H), 3.13 (m, 4H), 2.74 (br s, 6H), 2.14 (m, 2H).

EXAMPLE 219A

[0795] This example was made by substituting 2-phenoxyethylamine for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 219B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-phenoxyethyl)amino)benzenesulfonamide

[0796] This example was made by substituting EXAMPLE 219A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.89 (br s, 1H), 8.71 (t, 1H), 8.62 (d, 1H), 7.97 (dd, 1H), 7.73 (d, 2H), 7.52 (m, 1H), 7.47 (m, 4H), 7.37 (m, 3H), 7.26 (m, 3H), 6.94 (m, 3H), 6.88 (d, 2H), 4.24 (t, 2H), 3.84 (m, 2H), 3.42 (br s, 2H), 3.24 (m, 4H), 2.41 (m, 4H).

EXAMPLE 220A

[0797] This example was made by substituting EXAMPLE 19A for EXAMPLE 18A in EXAMPLE 218A.

EXAMPLE 220B

[0798] This example was made by substituting EXAMPLE 220A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 220C

[0799] This example was made by substituting EXAMPLE 220B for EXAMPLE 218B in EXAMPLE 218C.

EXAMPLE 220D

[0800] This example was made by substituting EXAMPLE 220C for EXAMPLE 218C in EXAMPLE 218D.

EXAMPLE 220E

[0801] This example was made by substituting EXAMPLE 83977F for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 220F

N-(4-(4-(.(4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-(((4-(trifluoromethoxy)phenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0802] This example was made by substituting EXAMPLE 220E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (br s, 1H), 8.55 (d, 1H), 8.26 (d, 1H), 7.90 (dd, 1H), 7.76 (d, 2H), 7.51 (d, 3H), 7.41 (d, 2H), 7.33 (m, 3H), 7.24 (d, 1H), 7.13 (d, 2H), 6.92 (d, 2H), 4.23 (m, 1H), 3.96 (br s, 2H), 3.61 (br s, 4H), 3.19 (br s, 4H), 3.01 (br s, 2H), 2.16 (m, 2H).

EXAMPLE 221A

[0803] This example was made by substituting 4-methoxythiophenol for 4-(trifluoromethoxy)thiophenol and EXAMPLE 220C for EXAMPLE 218C in EXAMPLE 218D.

EXAMPLE 221B

[0804] This example was made by substituting EXAMPLE 221A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 221C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-methoxyphenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide

[0805] This example was made by substituting EXAMPLE 221B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 9.86 (br s, 1H), 8.56 (d, 1H), 8.25 (d, 1H), 7.87 (dd, 1H), 7.76 (d, 3H), 7.72 (br s, 1H), 7.51 (d, 4H), 7.40 (d, 2H), 7.33 (m, 1H), 7.18 (d, 2H), 7.12 (d, 1H), 6.92 (d, 2H), 6.74 (d, 2H), 4.10 (m, 3H), 3.95 (br s, 4H), 3.68 (s, 3H), 3.27 (br s, 4H), 3.17 (br s, 4H), 3.01 (br s, 3H), 2.15 (m, 2H).

EXAMPLE 222A

[0806] This example was made by substituting 4-methylthiophenol for 4-(trifluoromethoxy)thiophenol and EXAMPLE 220C for EXAMPLE 218C in EXAMPLE 218D.

EXAMPLE 222B

[0807] This example was made by substituting EXAMPLE 222A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 222C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-methylphenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide

[0808] This example was made by substituting EXAMPLE 222B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.92 (br s, 1H), 8.53 (d, 1H), 8.26 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.74 (m, 1H), 7.53 (m, 4H), 7.40 (d, 2H), 7.34 (m, 1H), 7.16 (d, 1H), 7.10 (d, 2H), 6.93 (m, 4H), 4.28 (br s, 2H), 4.16 (m, 1H), 3.96 (br s, 2H), 3.62 (br s, 4H), 3.34 (d, 2H), 3.18 (m, 4H), 3.01 (br s, 4H), 2.17 (m, 4H).

EXAMPLE 223A

[0809] This example was made by substituting EXAMPLE 23C for EXAMPLE 18C in EXAMPLE 18E.

EXAMPLE 223B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((2-thienylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0810] This example was made by substituting EXAMPLE 223A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (br s, 1H), 7.98 (d, 1H), 7.83 (dd, 1H), 7.73 (m, 3H), 7.63 (dd, 1H), 7.52 (d, 4H), 7.40 (d, 2H), 7.33 (m, 1H), 7.13 (m, 1H), 7.03 (m, 1H), 6.92 (d, 2H), 6.80 (d, 1H), 6.08 (d, 1H), 4.27 (br s, 4H), 3.85 (m, 2H), 3.17 (m, 4H), 3.06 (dd, 2H), 2.99 (m, 2H), 2.10 (m, 2H).

EXAMPLE 224A

[0811] This example was made by substituting 4-chlorothiophenol for 4-(trifluoromethoxy)thiophenol and EXAMPLE 220C for EXAMPLE 218C in EXAMPLE 218D.

EXAMPLE 224B

[0812] This example was made by substituting EXAMPLE 224A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 224C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yljmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-chlorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide

[0813] This example was made by substituting EXAMPLE 224B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, 1H), 8.34 (d, 1H), 7.85 (dd, 1H), 7.73 (d, 2H), 7.51 (m, 1H), 7.47 (m, 4H), 7.37 (m, 2H), 7.26 (m, 5H), 7.12 (d, 1H), 6.86 (d, 2H), 4.16 (br s, 1H), 3.53 (m, 4H), 3.39 (m, 4H), 2.45 (br s, 2H), 2.40 (m, 4H), 1.99 (m, 1H), 1.86 (m, 1H).

EXAMPLE 225A

[0814] This example was made by substituting 4-fluorothiophenol for 4-(trifluoromethoxy)thiophenol in EXAMPLE 218D.

EXAMPLE 225B

[0815] This example was made by subsituting EXAMPLE 225A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 225C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-(((4-fluorophenyl)sulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0816] This example was made by substituting EXAMPLE 225B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.35 (d, 1H), 8.04 (d, 1H), 7.73 (dd, 1H), 7.61 (d, 2H), 7.39 (m, 1H), 7.36 (br s, 4H), 7.24 (m, 4H), 7.13 (dd, 1H), 6.96 (t, 2H), 6.83 (d, 1H), 6.68 (d, 2H), 3.95 (m, 1H), 3.27 (br s, 2H), 3.02 (m, 4H), 2.87 (br s, 1H), 2.80 (br s, 1H), 2.49 (br s, 6H), 2.28 (m, 4H), 1.94 (m, 2H).

EXAMPLE 226A

[0817] This example was made by substituting 4-fluorothiophenol for 4-(trifluoromethoxy)thiophenol and EXAMPLE 220C for EXAMPLE 218C in EXAMPLE 218D.

EXAMPLE 226B

[0818] This example was made by substituting EXAMPLE 226A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 226C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-(((4-fluorophenyl)sulfanyl)methyl)-3-(morpholin-4-yl)propyl)amino)-3-nitrobenzenesulfonamide

[0819] This example was made by substituting EXAMPLE 226B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.61 (d, 1H), 8.42 (d, 1H), 7.94 (dd, 1H), 7.82 (d, 2H), 7.60 (m, 1H), 7.55 (m, 4H), 7.47 (m, 2H), 7.40 (m, 2H), 7.33 (m, 1H), 7.18 (d, 1H), 7.13 (t, 2H), 6.96 (d, 2H), 4.22 (br s, 1H), 3.65 (br s, 6H), 3.31 (m, 6H), 2.64 (br s, 4H), 2.54 (br s, 2H), 2.49 (m, 4H), 2.09 (m, 1H), 1.97 (m, 1H).

EXAMPLE 227A

[0820] This example was made by substituting tert-butyl-1-piperazine for EXAMPLE 1A in EXAMPLE 2A.

EXAMPLE 227B

[0821] This example was made by subsituting EXAMPLE 227A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 227C

[0822] This example was made by substituting EXAMPLE 227B for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 227D

[0823] A mixture of ethyl-2,4-difluorobenzoate (194 mg), EXAMPLE 227C (250 mg), and K_2CO_3 (420 mg) in DMSO (1.7 mL) at 125°C was stirred for 3 hours, cooled to 25°C, treated with dichloromethane, washed with water, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2-10% ethyl acetate/hexanes.

EXAMPLE 227E

[0824] This example was made by substituting EXAMPLE 227E for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 227F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0825] This example was made by substituting EXAMPLE 227E for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.92 (br s, 1H), 9.62 (br s, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.71 (br s, 1H), 7.50 (m, 5H), 7.40 (d, 2H), 7.33 (m, 1H), 7.24 (m, 2H), 7.15 (m, 4H), 6.76 (m, 2H), 4.21 (m, 2H), 3.40 (d, 3H), 3.15 (m, 4H), 2.75 (br s, 6H), 2.15 (m, 2H).

EXAMPLE 228A

[0826] A mixture of 1.5M LDA in cyclohexane (5.5 mL) and THF (7.5 mL) at -78°C was treated with tert-butyl-4-oxo-1-piperidinecarboxylate (1.5 g) in THF (7.5 mL), stirred for 25 minutes, treated with N-phenyl bis(trifluoromethanesulfonamide) (2.8 g) in THF (7.5 mL), stirred for 10 minutes, stirred for 3 hours at 0°C, and concentrated. The concentrate was was chromatographed on neutral alumina with 10% ethyl acetate/hexanes.

EXAMPLE 228B

[0827] A mixture of EXAMPLE 228A (480 mg), 4-ethoxycarbonylphenylboronic acid (308 mg), LiCl (182 mg), tetrakis(triphenylphosphinepalladium (82 mg), and 2M Na_2CO_3 (2 mL) in toluene (4.8 mL) at 90°C was stirred for 3 hours, cooled to 25°C, and treated with water and ethyl acetate. The extract was washed with water and brine and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2-5% ethyl acetate/hexanes.

EXAMPLE 228C

[0828] This example was made by substituting EXAMPLE 228B for EXAMPLE 21B in EXAMPLE 21C.

EXAMPLE 228D

[0829] This example was prepared substituting EXAMPLE 228C for EXAMPLE 1A in EXAMPLE 2A.

EXAMPLE 228E

[0830] This example was prepared by substituting EXAMPLE 228D for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 228F

[0831] This example was prepared by substituting EXAMPLE 228E for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 228G

N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0832] This example was made by substituting EXAMPLE 228F for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (br s, 1H), 8.30 (d, 1H), 8.04 (d, 1H,), 7.63 (m, 3H), 7.53 (m, 1H), 7.30 (m, 2H), 7.24 (d, 2H), 7.20 (d, 2H), 7.14 (d, 2H), 7.11 (m, 1H), 6.98 (m, 2H), 6.93 (d, 1H), 6.87 (m, 3H), 5.84 (br s, 1H), 4.13 (br s, 2H), 3.94 (m, 1H), 2.89 (m, 4H), 2.49 (br s, 6H), 2.24 (m, 2H), 1.89 (m, 2H).

EXAMPLE 229

N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0833] This example was made by substituting EXAMPLE 228F for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.07 (br s, 2H), 8.56 (d, 1H), 8.30 (d, 1H), 7.89 (d, 3H), 7.79 (m, 1H), 7.55 (m, 2H), 7.50 (m, 2H), 7.45 (d, 2H), 7.40 (m, 2H), 7.36 (m, 1H), 7.24 (m, 2H), 7.19 (d, 1H), 7.13 (m, 3H), 6.10 (br s, 1H), 4.39 (br s, 2H), 4.20 (m, 1H), 3.95 (br s, 3H), 3.40 (m, 4H), 3.18 (m, 4H), 3.02 (br s, 2H), 2.65 (br s, 1H), 2.54 (s, 3H), 2.18 (m, 2H).

EXAMPLE 230

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)-2-fluorobenzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0834] This example was prepared by substituting EXAMPLE 227E for EXAMPLE 2C and EXAMPLE 18F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, 1H), 7.71 (dd, 1H), 7.57 (t, 1H), 7.51 (m, 1H), 7.47 (br s, 4H), 7.38 (m, 4H), 7.32 (m, 2H), 7.23 (m, 2H), 6.62 (d, 2H), 6.53 (dd, 1H), 3.83 (m, 1H), 3.38 (br s, 2H), 3.23 (m, 2H), 3.16 (m, 4H), 2.91 (br s, 1H), 2.74 (br s, 1H), 2.52 (br s, 6H), 2.37 (m, 4H), 2.01 (m, 2H). EXAMPLE 231A

[0835] A mixture of methyl-6-chloronicotinate (250 mg), EXAMPLE 227C (458 mg), TEA (0.24 mL), and acetonitrile (1.5 mL) at 95°C was stirred for 10 hours, cooled to 25°C, treated with dichloromethane, washed with water, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-2% methanol dichloromethane.

EXAMPLE 231B

[0836] This example was made by substituting EXAMPLE 231A for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 231C

N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0837] This example was made by substituting EXAMPLE 231B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.31 (br s, 1H), 8.36 (d, 1H), 8.28 (d, 1H), 8.03 (d, 1H), 7.72 (dd, 1H), 7.61 (dd, 1H), 7.47 (br s, 1H), 7.25 (d, 4H), 7.13 (d, 2H), 7.06 (m, 1H), 6.98 (m, 2H), 6.89 (m, 4H), 6.60 (d, 1H), 3.94 (m, 4H), 2.88 (m, 4H), 2.49 (br s, 6H), 2.24 (m, 2H), 1.89 (m, 2H).

EXAMPLE 232A

[0838] This example was made by substituting 1-benzyl-4-piperidone for tert-butyl-4-oxo-1-piperidinecarboxylate in EXAMPLE 228A.

EXAMPLE 232B

[0839] This example was made by substituting EXAMPLE 232A for EXAMPLE 228A in EXAMPLE 228B.

EXAMPLE 232C

[0840] A mixture of EXAMPLE 232B (0.98 g) and 10%Pd/C (0.1 g) in ethanol (50 mL) at 50°C was stirred under hydrogen for 2 hours, cooled to 25°, filtered, and concentrated.

EXAMPLE 232D

[0841] This example was prepared by substituting EXAMPLE 232C for EXAMPLE 1A in EXAMPLE 2A.

EXAMPLE 232E

[0842] This example was made by substituting EXAMPLE 232D for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 232F

[0843] This example was made by substituting EXAMPLE 232E for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 232G

N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0844] This example was made by substituting EXAMPLE 232F for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (br s, 1H), 9.46 δ (br s, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.83 (d, 2H), 7.79 (m, 1H), 7.55 (m, 4H), 7.40 (d, 2H), 7.35 (m, 1H), 7.28 (d, 2H), 7.23 (d, 2H), 7.14 (m, 4H), 4.32 (br s, 2H), 4.19 (m, 2H), 3.39 (d, 2H), 3.29 (d, 2H), 3.13 (m, 2H), 2.81 (br s, 2H), 2.74 (br s, 6H), 2.14 (m, 2H), 1.84 (m, 3H).

EXAMPLE 233

N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0845] This example was made by substituting EXAMPLE 232F for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.98 (m, 1H), 9.51 (br s, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 7.87 (dd, 1H), 7.83 (d, 2H), 7.79 (m, 1H), 7.56 (m, 4H), 7.40 (d, 2H), 7.35 (m, 1H), 7.28 (d, 2H), 7.24 (d, 2H), 7.14 (m, 4H), 4.32 (br s, 2H), 4.19 (m, 1H), 3.93 (br s, 2H), 3.39 (d, 4H), 3.29 (d, 3H), 3.18 (br s, 3H), 3.02 (br s, 2H), 2.80 (m, 3H), 2.17 (m, 2H), 1.84 (m, 3H).

EXAMPLE 234

N-(4-(1-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0846] This example was prepared by substituting EXAMPLE 228F for EXAMPLE 2C and EXAMPLE 18F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.32 (br s, 1H), 7.72 (d, 1H), 7.62 (d, 2H), 7.59 (dd, 1H), 7.53 (br s, 1H), 7.29 (m, 2H), 7.25 (d, 2H), 7.20 (d, 2H), 7.16 (d, 2H), 7.11 (m, 1H), 7.04 (m, 4H), 6.94 (t, 1H), 6.63 (d, 1H), 5.86 (br s, 1H), 5.78 (d, 1H), 4.11 (br s, 1H), 3.69 (m, 1H), 2.90 (m, 2H), 2.75 (m, 2H), 2.4.9 (s, 6H), 2.25 (m, 2H), 1.86 (m, 2H).

EXAMPLE 235

N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0847] This example was made by substituting EXAMPLE 231B for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.91 (br s, 1H), 8.61 (d, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 7.98 (dd, 1H), 7.87 (dd, 1H), 7.74 (br s, 1H), 7.51 (d, 4H), 7.39 (d, 2H), 7.33 (m, 1H), 7.24 (m, 2H), 7.19 (d, 1H), 7.13 (m, 3H), 6.86 (d, 1H), 4.33 (br s, 2H), 4.20 (m, 2H), 3.96 (br s, 4H), 3.62 (br s, 4H), 3.40 (m, 4H), 3.19 (m, 3H), 3.01 (br s, 2H), 2.80 (br s, 2H), 2.17 (m, 2H).

EXAMPLE 236

N-((6-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-3-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0848] This example was prepared by substituting EXAMPLE 231B for EXAMPLE 2C and EXAMPLE 18F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (br s, 1H), 8.60 (d, 1H), 7.95 (m, 1H), 7.82 (dd, 1H), 7.73 (br s, 1H), 7.51 (d, 3H), 7.39 (d, 2H), 7.30 (m, 4H), 7.19 (m, 1H), 6.88 (d, 1H), 6.85 (d, 1H), 6.04 (d, 1H), 3.94 (m, 1H), 3.29 (m, 4H), 3.15 (m, 2H), 3.01 (m, 2H), 2.74 (s, 6H), 2.11 (m, 2H).

EXAMPLE 237A

[0849] 2.5M n-Butyllithium in hexanes (3 mL) at 25°C was treated with methyltriphenylphosphonium bromide (2.6 g) in diethyl ether (37 mL), stirred for 1.5 hours, treated with ethyl 4-(4-oxopiperidin-1-yl)benzoate, prepared as described in Synthesis 1981, 8, 606, (1.47 g), in diethyl ether (15 mL), stirred for 18 hours, and filtered. The filtrate was washed with water and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 237B

[0850] A mixture of EXAMPLE 237A (400 mg) and 0.5M 9-BBN (3.3 mL) in THF (2 mL) at 60°C was stirred for 1.5 hours, cooled to 25°C, treated dropwise with 2-bromo-4'-chlorobiphenyl (434 mg), K_2CO_3 (296 mg), and dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane (24.5 mg) in water (0.36 mL) and DMF (3.6 mL), stirred for 3 hours at 60°C, cooled to 25°C, and treated with water and ethyl acetate. The extract was washed with brine and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 2-5% ethyl acetate/hexanes.

EXAMPLE 237C

[0851] This example was made by substituting EXAMPLE 237B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 237D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0852] This example was made by substituting EXAMPLE 237C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (br s, 1H), 9.43 (br s, 1H), 8.54 (d, 1H), 7.87 (dd, 1H), 7.70 (d, 2H), 7.47 (d, 2H), 7.32 (m, 3H), 7.27 (dd, 1H), 7.25 (d, 2H), 7.17 (m, 3H), 7.11 (m, 2H), 6.84 (d, 2H), 4.20 (m, 1H), 3.78 (d, 2H), 3.39 (d, 2H), 3.14 (m, 2H), 2.74 (s, 6H), 2.65 (t, 2H), 2.53 (m, 2H), 2.14 (m, 2H), 1.55 (m, 1H), 1.44 (d, 2H), 0.96 (m, 2H).

EXAMPLE 238

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperidin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0853] This example was made by substituting EXAMPLE 237C for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.95 (br s, 1H), 9.75 (br s, 1H), 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.70 (d, 2H), 7.48 (m, 2H), 7.32 (m, 4H), 7.28 (m, 1H), 7.25 (m, 2H), 7.17 (m, 4H), 7.11 (m, 1H), 6.84 (d, 2H), 4.19 (m, 1H), 3.96 (br s, 2H), 3.78 (d, 4H), 3.40 (d, 4H), 3.20 (m, 2H), 3.02 (br s, 2H), 2.66 (t, 2H), 2.53 (m, 2H), 2.17 (m, 2H), 1.56 (m, 1H), 1.45 (d, 2H), 0.98 (m, 2H).

EXAMPLE 239A

[0854] A mixture of, 2,5-dibromopyridine(2.4 g), dichloro(1,1'-bis(diphenylphosphino)ferrocene)palladium(II) dichloromethane (430 mg), and TEA (2.9 mL) in methanol (10 mL), and DMF (10 mL) in a Parr shaker at 50°C was stirred under CO (200 psi) over 5.5 hours, cooled to 25°C, filtered, and concentrated. The concentrate was flash chromatographed on silca gel with 10-20% ethyl acetate/hexanes.

EXAMPLE 239B

[0855] A mixture of EXAMPLE 239A (900 mg), EXAMPLE 227C (1.6 g), and DIEA (2.1 mL) in DMSO (5.9 mL) was stirred at 130°C for 24 hours, cooled to 25°C, and concentrated. The concentrate was flash chromatagraphed on silica gel with 30-50% ethyl acetate/hexanes.

EXAMPLE 239C

[0856] This example was made by substituting EXAMPLE 239B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 239D

N-((5-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-2-yl)carbonyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0857] This example was made by substituting EXAMPLE 239C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (br s, 1H), 8.59 (d, 1H), 8.30 (m, 2H), 7.90 (dd, 1H), 7.82 (d, 1H), 7.70 (br s, 1H), 7.51 (m, 4H), 7.41 (d, 2H), 7.38 (dd, 1H), 7.32 (m, 1H), 7.22 (d, 2H), 7.17 (d, 1H), 7.12 (m, 3H), 4.19 (m, 2H), 3.39 (d, 2H), 3.13 (m, 4H), 2.74 (s, 6H), 2.14 (m, 2H).

EXAMPLE 240

N-((5-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)pyridin-2-yl)carbonyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0858] This example was made by substituting EXAMPLE 239C for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H

NMR (500 MHz, DMSO-d_6) δ 9.89 (br s, 1H), 8.59 (d, 1H), 8.30 (m, 2H), 7.91 (dd, 1H), 7.83 (d, 1H), 7.73 (br s, 1H), 7.52 (d, 4H), 7.40 (m, 3H), 7.34 (m, 1H), 7.23 (d, 2H), 7.18 (d, 1H), 7.12 (m, 3H), 4.20 (m, 2H), 3.96 (br s, 4H), 3.40 (d, 2H), 3.19 (m, 2H), 3.01 (br s, 4H), 2.17 (m, 2H).

EXAMPLE 241A

[0859] EXAMPLE 855947A (12.3 g) in propan-2-ol (57 mL) at 0°C was treated with $NaBH_4$ (2.2 g) in 1:1 ethanol/propane-2-ol (100 mL), stirred at 25°C for 18 hours, treated with NH_4Cl and brine, and extracted with diethyl ether. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10-30% ethyl acetate/hexanes.

EXAMPLE 241B

[0860] This example was made by substituting EXAMPLE 241A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 241C

[0861] A mixture of EXAMPLE 241B (420 mg) and TEA (0.95 mL) in dichloromethane (8.7 mL) at 0°C was treated with methanesulfonyl chloride (0.16 mL), stirred for 0.5 hours, treated with EXAMPLE 228C (0.57 g), stirred for 1 hour at 0°C and for 5 hours at 25°C, treated with dichloromethane, washed with water and brine, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-2% methanol/dichloromethane.

EXAMPLE 241D

[0862] This example was made by substituting EXAMPLE 241C for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 241E

N-(4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0863] This example was made by substituting EXAMPLE 241D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) 5 8.47 (d, 1H), 8.17 (d, 1H), 7.82 (m, 3H), 7.38 (d, 2H), 7.31 (d, 4H), 7.24 (m, 2H), 7.18 (m, 1H), 7.14 (m, 2H), 6.90 (d, 1H), 6.13 (br s, 1H), 4.07 (m, 1H), 2.93 (m, 6H), 2.61 (m, 6H), 2.39 (br s, 2H), 2.24 (m, 2H), 2.08 (m, 2H), 1.99 (m, 2H), 1.44 (t, 2H), 0.97 (br s, 2H).

EXAMPLE 242A

[0864] This example was made by substituting 2-bromo-cyclohex-1-enecarboxaldehyde, prepared as described in Collect. Czech. Chem. Commun. 1961, 26, 3059-3073, for EXAMPLE 855947A in EXAMPLE 241A.

EXAMPLE 242B

[0865] This example was made by substituting EXAMPLE 242A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 242C

[0866] This example was made by substituting EXAMPLE 242B for EXAMPLE 241B in EXAMPLE 241C.

EXAMPLE 242D

[0867] This example was made by substituting EXAMPLE 242C for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 242E

N-(4-(1-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0868] This example was made by substituting EXAMPLE 242D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.69 (br s, 1H), 9.60 (br s, 1H), 8.56 (d, 1H), 8.30 (d, 1H), 7.89 (m, 3H), 7.45 (d, 2H), 7.37 (m, 2H), 7.17 (m, 8H), 6.14 (br s, 1H), 4.20 (m, 1H), 3.89 (m, 1H), 3.66 (d, 4H), 3.40 (d, 3H), 3.12 (m, 4H), 2.75 (br s, 6H), 2.69 (br s, 1H), 2.29 (br s, 2H), 2.22 (br s, 2H), 2.15 (m, 2H), 1.71 (br s, 4H).

EXAMPLE 243

N-(4-(1-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0869] This example was made by substituting EXAMPLE 242D for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (br s, 1H), 9.60 (br s, 1H), 8.56 (d, 1H), 8.30 (d, 1H), 7.89 (m, 3H), 7.45 (d, 2H), 7.37 (m, 2H), 7.24 (m, 2H), 7.15 (m, 6H), 6.13 (br s, 1H), 4.20 (m, 1H), 3.92 (m, 2H), 3.64 (m, 4H), 3.19 (m, 4H), 3.02 (br s, 4H), 2.70 (m, 2H), 2.29 (br s, 2H), 2.18 (m, 4H), 1.71 (br s, 4H).

EXAMPLE 244

N-(4-(1-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)-1,2,3,6-tetrahydropyridin-4-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0870] This example was made by substituting EXAMPLE 241D for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (d, 1H), 8.27 (d, 1H), 7.84 (d, 2H), 7.79 (dd, 1H), 7.39 (d, 2H), 7.32 (m, 4H), 7.24 (t, 2H), 7.16 (m, 3H), 6.93 (d, 1H), 6.10 (br s, 1H), 4.09 (m, 1H), 3.55 (br s, 4H), 3.34 (m, 4H), 3.02 (m, 2H), 2.76 (s, 1H), 2.27 (m, 2H), 2.01 (br s, 3H), 1.86 (m, 1H), 1.46 (t, 2H), 0.98 (s, 6H).

EXAMPLE 245A

[0871] This example was made by substituting 1,4-cyclohexanedione monoethylene ketal for ethyl 4-(4-oxopiperidin-1-yl)benzoate in EXAMPLE 237A.

EXAMPLE 245B

[0872] This example was made by substituting EXAMPLE 245A for EXAMPLE 237A in EXAMPLE 237B.

EXAMPLE 245C

[0873] A mixture of EXAMPLE-245B (1.9 g) and 35% aqueous TFA (42 mL) in chloroform (61 mL) was stirred at 25°C for 7 hours and treated with water and dichloromethane. The extract was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$), filtered, and concentrated.

EXAMPLE 245D

[0874] This example was made by substituting EXAMPLE 245C for tert-butyl-4-oxo-1-piperidinecarboxylate and by substituting 2-(N,N-bis(trifluoromethylsulfonyl)amino)-5-chloropyridine for N-phenylbis(trifluoromethanesulfonamide) in EXAMPLE 228A.

EXAMPLE 245E

[0875] This example was made by substituting EXAMPLE 245D for EXAMPLE 228A in EXAMPLE 228B.

EXAMPLE 245F

[0876] This example was made by substituting EXAMPLE 245E for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 245G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)-1-cyclohexen-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0877] This example was made by substituting EXAMPLE 245F for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.45 (br s, 1H), 8.56 (d, 1H), 8.30 (d, 1H), 7.88 (dd, 1H), 7.81 (d, 2H), 7.47 (d, 2H), 7.42 (d, 2H), 7.34 (m, 3H), 7.32 (s, 1H), 7.28 (m, 1H), 7.24 (m, 2H), 7.16 (m, 4H), 7.11 (m, 1H), 6.16 (br s, 1H), 4.19 (m, 1H), 3.14 (m, 3H), 2.74 (s, 6H), 2.61 (m, 2H), 2.24 (m, 2H), 2.14 (m, 2H), 2.03 (m, 1H), 1.68 (m, 3H), 1.17 (m, 1H).

EXAMPLE 246

N-(4-(4-((4'-chloro(1,1'-biphenyl)- 2-yl)methyl)-1-cyclohexen-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0878] This example was made by substituting EXAMPLE 245F for EXAMPLE 2C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.79 (d, 2H), 7.46 (d, 2H), 7.40 (d, 2H), 7.32 (m, 4H), 7.27 (m, 1H), 7.23 (m, 2H), 7.15 (m, 4H), 7.10 (m, 1H), 6.14 (br s, 1H), 4.18 (m, 1H), 3.77 (br s, 4H), 3.15 (m, 4H), 2.59 (m, 2H), 2.20 (m, 4H), 2.02 (d, 1H), 1.67 (m, 3H), 1.15 (m, 1H).

EXAMPLE 247A

[0879] This example was made by substituting methyl-4-fluorobenzoate for ethyl-2,4-difluorobenzoate and cis-octahydropyrrolo[3,4-c]pyrrole for EXAMPLE 227C in EXAMPLE 227D.

EXAMPLE 247B

[0880] This example was made by substituting EXAMPLE 247A for EXAMPLE 1A in EXAMPLE 2A.

EXAMPLE 247C

[0881] This example was made by substituting EXAMPLE 247B for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 247D

[0882] This example was made by substituting EXAMPLE 247C for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 247E

N-(4-((3aR,6aS)-5-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)hexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0883] This example was made by substituting EXAMPLE 247D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 8.34 (d, 1H), 7.96 (d, 1H), 7.92 (br s, 1H), 7.65 (brs, 2H), 7.49 (m, 4H), 7.38 (br s, 2H), 7.30 (m, 2H), 7.19 (m, 6H), 6.83 (m, 1H), 6.46 (m, 2H), 4.34 (br s, 2H), 3.84 (m, 1H), 3.28 (m, 4H), 3.15 (m, 4H), 2.80 (m, 6H), 2.41 (br s, 2H).

EXAMPLE 248A

[0884] A mixture of 4-chloro-3-nitrobenzenesulfonyl chloride (10 g), TEA (10.87 mL), and bis(2,4-dimethoxybenzyl)amine (12.38 g) in dichloromethane (200 mL) at 25°C was stirred for 12 hours, treated with dichloromethane (200 mL), washed with saturated sodium bicarbonate (100 mL) and brine, and concentrated.

EXAMPLE 248B

[0885] A mixture of EXAMPLE 248A (20.98 g) and 2M methylamine in THF (400 mL) at 80°C was stirred for 4 hours and concentrated. The concentrate was treated with ethyl acetate and saturated sodium bicarbonate. The extract was dried (Mg_2SO_4), filtered and concentrated.

EXAMPLE 248C

[0886] A mixture of EXAMPLE 248B (1 g) and 3.56 mmol/g polymer-supported N,N-DIEA (2.65 g) in dichloromethane (10 mL) was treated with 20% phosgene in toluene (10.1 mL), heated at 40°C for 24 hours, filtered and concentrated.

EXAMPLE 248D

[0887] A mixture of EXAMPLE 248C (200 mg), TEA (141 μL) and N-methyl-4-trifluoromethoxyphenyl aniline (129 mg) in dichloromethane (2 mL) at 50°C was heated for 12 hours and concentrated. The concentrate was flash chromatographed on silica gel with 70% ethyl acetate/hexane.

EXAMPLE 248E

[0888] EXAMPLE 248D (57 mg) in triethylsilane/TFA/dichloromethane (0.05 mL/0.45 mL/0.5 mL) was stirred at 25°C for 30 minutes and concentrated. The concentrate was flash chromatographed on silica gel with 80% ethyl acetate/hexane.

EXAMPLE 248F

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl-4-(trifluoromethoxy)anilino)carbonyl)amino)-3-nitrobenzenesulfonamide

[0889] This example was made by substituting EXAMPLE 248E for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) δ 8.26 (d, 1H), 7.80 (d, 2H), 7.72 (br, 1H), 7.41 (m, 8H), 7.28 (d, 1H), 6.92 (m, 6H), 4.26 (br, 2H), 3.74 (br, 2H), 3.13 (br, 2H), 2.96 (s, 6H), 2.82 (br, 2H)

EXAMPLE 249A

[0890] This example was made by substituting N-methyl-2-methylanaline for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 249B

[0891] This example was made by substituting EXAMPLE 249A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 249C

N-(4-(9-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((2-dimethylanilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0892] This example was made by substituting EXAMPLE 249B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) 8.30 (d, 1H), 7.86 (d, 1H), 7.83 (d, 2H), 7.75 (br, 1H), 7.53 (m, 2H), 7.47 (d, 2H), 7.43 (q, 1H), 7.37 (m, 3H), 7.21 (d, 1H), 6.97 (d, 2H), 6.83 (d, 1H), 6.74 (t, 1H), 6.64 (t, 1H), 6.56 (d, 1H), 4.31 (br, 2H), 3.80 (br, 2H), 3.18 (s, 3H), 3.14 (br, 2H), 2.90 (s, 3H), 2.84 (br, 4H), 1.95 (s, 3H).

EXAMPLE 250A

[0893] This example was made by substituting N-methyl-4-methoxyanaline for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 250B

[0894] This example was made by substituting EXAMPLE 250A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 250C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((4-methoxy(methyl)anilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0895] This example was made by substituting EXAMPLE 250B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE ID. 1H NMR (400MHz, DMSO-d_6) δ 8.28 (d, 1H), 7.86 (dd, 1H), 7.81 (d, 2H), 7.73 (br, 1H), 7.52 (br, 2H), 7.47 (d, 2H), 7.43 (d, 1H), 7.36 (m, 3H), 7.20 (d, 1H), 6.94 (d, 2H), 6.70 (d, 2H), 6.49 (d, 2H), 4.28 (br, 2H), 3.81 (br, 2H), 3.43 (s, 3H), 3.19 (s, 3H), 3.14 (br, 2H), 2.90 (s, 3H), 2.82 (br, 4H).

EXAMPLE 251A

[0896] This example was made by substituting N-methyl-4-methylanaline for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 251B

[0897] This example was made by substituting EXAMPLE 251A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 251C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((4-dimethylanilino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0898] This example was made by substituting EXAMPLE 251B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) δ 8.25 (d, 1H), 7.83 (m, 3H), 7.73 (br, 1H), 7.52 (m, 2H), 7.47 (d, 2H), 7.42 (d, 1H), 7.36 (m, 3H), 7.20 (d, 1H), 6.96 (d, 2H), 6.71 (d, 2H), 6.66 (d, 2H)', 4.28 (br, 2H), 3.80 (br, 2H), 3.22 (s, 3H), 3.14 (br, 2H), 2.91 (s, 3H), 2.82 (br, 4H), 1.90 (s, 3H)

EXAMPLE 252A

[0899] This example was made by substituting N-diphenylmethyl methylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 252B

[0900] This example was made by substituting EXAMPLE 252A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 252C

4-(((benzhydryl(methyl)amino)carbonyl)(methyl)amino)-N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0901] This example was made by substituting EXAMPLE 252B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE ID. 1H NMR (400MHz, DMSO-d_6) δ 8.35 (d, 1H), 8.15 (dd, 1H), 7.74 (dd, 4H), 7.50 (m, 4H), 7.43 (d, 1H), 7.36 (m, 6H), 7.29 (m, 2H), 7.16 (d, 4H), 6.92 (d, 2H), 6.30 (s, 1H), 4.33 (br, 2H), 3.84 (br, 4H), 3.25 (s, 3H), 3.13 (br, 3H), 2.82 (br, 2H), 2.69 (s, 3H).

EXAMPLE 253A

[0902] This example was made by substituting (S)-(-)-N-methyl-1-phenethylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 253B

[0903] This example was made by substituting EXAMPLE 253A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 253C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl((1S)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide

[0904] This example was made by substituting EXAMPLE 253B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE ID. 1H NMR (400MHz, DMSO-d_6) δ 8.38 (d, 1H), 8.19 (dd, 1H), 7.76 (d, 2H), 7.70 (d, 1H), 7.50 (br, 6H), 7.33 (br, 8H), 6.93 (d, 2H), 5.17 (q, 1H), 4.37 (br, 2H) 3.84 (br, 2H), 3.26 (s, 3H), 3.11 (br, 4H), 2.84 (br, 2H), 2.61 (s, 3H), 1.46 (d, 3H)

EXAMPLE 254A

[0905] This example was made by substituting 2-(4-methylpiperazinyl)-1-phenethyl methylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 254B

[0906] This example was made by substituting EXAMPLE 254A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 254C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl(2-(4-methylpiperazin-1-yl)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide

[0907] This example was made by substituting EXAMPLE 254B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) δ 8.37 (d, 1H), 8.20 (dd, 1H), 7.76 (d, 3H), 7.65 (d, 1H), 7.48 (m, 5H), 7.34 (m, 8H), 6.93 (d, 2H), 5.31 (dd, 1H), 4.36 (br, 2H), 3.84 (br, 2H), 3.42 (br, 4H), 3.30 (s, 3H), 3.07 (br, 8H), 2.86 (m, 2H), 2.80 (s, 3H), 2.75 (s, 3H), 2.33 (m, 2H).

EXAMPLE 255A

[0908] This example was made by substituting 2-morpholine-4-yl-1-phenethyl methylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 255B

[0909] This example was made by substituting EXAMPLE 255A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 255C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(methyl((methyl(2-(morpholin-4-yl)-1-phenylethyl)amino)carbonyl)amino)-3-nitrobenzenesulfonamide

[0910] This example was made by substituting EXAMPLE 255B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) δ 8.40 (d, 1H), 8.15 (dd, 1H), 7.76 (m, 3H), 7.66 (d, 1H), 7.47 (m, 13H), 6.93 (d, 2H), 5.57 (br, 1H), 4.37 (br, 2H), 3.83 (br, 8H), 3.25 (s, 3H), 3.13 (br, 6H), 2.84 (br, 4H), 2.64 (s, 3H)

EXAMPLE 256A

[0911] This example was made by substituting (1,2-diphenyl-ethyl)methylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 256B

[0912] This example was made by substituting EXAMPLE 256A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 256C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((((1,2-diphenylethyl)(methyl)amino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0913] This example was made by substituting EXAMPLE 256B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (400MHz, DMSO-d_6) δ 8.33 (d, 1H), 8.05 (dd, 1H), 7.75 (d, 3H), 7.38 (m, 18H), 7.22 (m, 1H), 6.92 (d, 2H), 5.58 (dd, 1H), 4.32 (br, 2H), 3.65 (br, 6H), 3.40 (dd, 1H), 3.22 (dd, 1H), 3.10 (br, 2H), 2.69 (s, 3H), 2.66 (s, 3H)

EXAMPLE 257A

[0914] This example was made by substituting (2-(methylamino)-2-phenylethyl)dimethylamine for N-methyl-4-trifluoromethoxyaniline in EXAMPLE 248D.

EXAMPLE 257B

[0915] This example was made by substituting EXAMPLE 257A for EXAMPLE 248D in EXAMPLE 248E.

EXAMPLE 257C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((((2-(dimethylamino)-1-phenylethyl)(methyl)amino)carbonyl)(methyl)amino)-3-nitrobenzenesulfonamide

[0916] This example was made by substituting EXAMPLE 257B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. 1H NMR (500MHz, DMSO-d_6) δ 8.39 (d, 1H), 8.12 (dd, 1H), 7.74 (d, 3H), 7.64 (d, 1H), 7.40 (m, 13H), 6.91 (d, 2H), 5.54 (dd, 1H), 4.00 (br, 8H), 3.25 (s, 3H), 3.14 (br, 2H), 2.69 (s, 6H), 2.61 (s, 3H)

EXAMPLE 258

3-amino-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0917] A mixture of EXAMPLE 10 (400 mg) and 30% Pd/C (120 mg) in 1:1 methanol/ethyl acetate (10 mL) at 25°C was stirred under H_2 (balloon) for 2 hours and filtered. The filtrate was concentrated and flash chromatographed on silica gel with 40% acetonitrile/dichloromethane. 1H NMR (500MHz, $CDCl_3$) δ 7.87 (br, 1H), 7.64 (m, 2H), 7.40 (m, 6H), 7.17 (m, 8H), 6.38 (br, 1H), 5.17 (br, 4H), 4.29 (s, 2H), 3.30 (m, 4H), 2.95 (s, 2H), 2.49 (br, 2H)

EXAMPLE 259

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-(2-(phenylsulfanyl)ethyl)-1H-1,2,3-benzotriazole-5-sulfonamide

[0918] A mixture of EXAMPLE 258 (50 mg) and sodium nitrite (7.2 mg) in water/hydrochloric acid/acetic acid (0.38 mL/0.562 mL/2 mL) at 0°C was stirred for 2 hours and concentrated. The concentrate in 1:1 DMSO/methanol (10.5 mL) and purified by HPLC with 0-70% acetonitrile/ water with 0.1% TFA. ^{1}H NMR (500MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.23 (dd, 1H), 7.78 (dd, 1H), 7.69 (d, 2H), 7.49 (m, 3H), 7.42 (d, 2H), 7.30 (m, 1H), 7.26 (m, 2H), 7.19 (m, 5H), 5.66 (d, 2H), 4.82 (t, 2H), 4.39 (s, 2H), 3.50 (t, 2H), 3.42 (br, 8H)

EXAMPLE 260

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-1-(2-(phenylsulfanyl)ethyl)-1H-benzimidazole-5-sulfonamide

[0919] EXAMPLE 258 (60 mg) in formic acid (2 mL) was heated at 100°C for 3 hours, and concentrated. The concentrate was purified by HPLC with 0-70% acetonitrile/water with 0.1% TFA. 1H NMR (400MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.46 (s, 1H), 8.13 (d, 1H), 7.75 (dd, 1H), 7.62 (d, 2H), 7.46 (m, 4H), 7.30 (dd, 1H), 7.16 (m, 8H), 6.63 (d, 2H), 4.48 (t, 2H), 4.35 (s, 2H), 3.42 (br, 4H), 3.35 (t, 2H), 3.00 (br, 4H).

EXAMPLE 261

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide

[0920] This example was made by substituting EXAMPLE 90C and 4-(cyclohexylmethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (m, 1H), 8.61 (m, 1H), 7.91 (dd, 1H), 7.67 (d, 2H), 7.44 (m, 1H), 7.39 (m, 1H), 7.34 (m, 2H), 7.30 (m, 2H), 7.27 (m, 2H), 7.22 (m, 1H), 7.16 (m, 1H), 6.80 (m, 2H), 3.38 (m, 2H), 3.27 (m, 3H), 3.03 (s, 3H), 2.89 (s, 2H), 2.84 (m, 1H), 2.76 (m, 1H), 1.77 (m, 1H), 1.66 (m, 5H), 1.47 (m, 2H), 1.08 (m, 7H).

EXAMPLE 262

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(cyclohexylamino)-3-nitrobenzenesulfonamide

[0921] This example was made by substituting EXAMPLE 90C and 4-(cyclohexylamino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.62 (d, 1H), 8.31 (d, 1H), 7.92 (dd, 1H), 7.66 (d, 2H), 7.34 (m, 9H), 7.15 (m, 1H), 6.79 (d, 2H), 3.71 (m, 1H), 3.39 (d, 2H), 3.02 (m, 3H), 2.84 (m, 4H), 1.94 (m, 2H), 1.65 (m, 3H), 1.30 (m, 9H).

EXAMPLE 263

N-(4-(9-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0922] This example was made by substituting EXAMPLE 90C and 4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.96 (m, 1H), 8.51 (m, 2H), 7.82 (dd, 1H), 7.71 (d, 2H), 7.33 (m, 11H), 7.15 (m, 1H), 7.00 (m, 2H), 6.92 (m, 1H), 6.82 (d, 2H), 3.54 (s, 2H), 3.40 (m, 2H), 3.03 (s, 3H), 2.85 (m, 4H), 1.57 (s, 6H), 1.46 (m, 2H), 1.17 (m, 2H).

EXAMPLE 264A

[0923] A mixture of thiophenol (0.2 mL), (1-amino-cyclopentyl)methanol (0.2 g), tributylphosphine (0.5 mL), and THF (30 mL) at 0°C was treated with ADDP (0.482g), stirred for 1 hour, stirred at 25°C for 18 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes and 5% methanol/dichloromethane.

EXAMPLE 264B

[0924] This example was prepared by substituting EXAMPLE 264A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 264C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[0925] This example was made by substituting EXAMPLE 264B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.50 (s, 1H), 8.42 (s, 1H), 8.35 (d, 1H), 7.74 (m, 4H), 7.39 (m, 8H), 7.11 (m, 3H), 6.79 (m, 5H), 4.33 (s, 1H), 3.81 (s, 1H), 3.50 (s, 2H), 3.07 (m, 4H), 2.35 (m, 4H), 1.98 (m, 4H), 1.64 (m, 4H).

EXAMPLE 265

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[0926] This example was made by substituting EXAMPLE 90C and EXAMPLE 264B for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.96 (s, 1H), 8.49 (s, 1H), 8.41 (d, 1H), 7.82 (dd, 1H), 7.73 (d, 1H), 7.34 (m, 8H), 7.16 (m, 4H), 6.83 (m, 5H), 3.57 (s, 2H), 3.31 (s, 2H), 3.02 (s, 3H), 2.85 (m, 4H), 2.11 (m, 2H), 1.99 (m, 2H), 1.71 (m, 4H), 1.47 (m, 2H), 1.18 (m, 2H).

EXAMPLE 266

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[0927] This example was made by substituting EXAMPLE 264B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.52 (d, 1H), 7.85 (m, 3H), 7.72 (m, 1H), 7.58 (m, 2H), 7.51 (d, 2H), 7.42 (m, 1H), 7.35 (d, 2H), 7.12 (m, 2H), 6.99 (m, 3H), 6.72 (m, 3H), 4.46 (s, 2H), 3.50 (s, 2H), 3.31 (m, 4H), 3.17 (m, 4H), 2.13 (m, 4H), 1.80 (m, 4H).

EXAMPLE 267A

[0928] A mixture of (S)-2-aminobutan-1-ol (1 g), tributylphosphine (3 mL) and phenyl disulfide (2.64 g) in toluene (20 mL) at 85°C was stirred for 16 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 1% methanol/dichloromethane.

EXAMPLE 267B

[0929] This example was prepared by substituting EXAMPLE 267A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 267C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0930] This example was made by substituting EXAMPLE 267B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.30 (d, 1H), 7.90 (dd, 1H), 7.75 (d, 2H), 7.52 (m, 1H), 7.38 (m, 6H), 7.24 (m, 3H), 7.05 (m, 2H), 6.96 (d, 1H), 6.90 (d, 2H), 3.95 (m, 1H), 3.54 (s, 2H), 3.27 (m, 4H), 2.51 (m, 4H), 1.81 (m, 2H), 1.00 (t, 3H).

EXAMPLE 268

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-(((1S)-1-((phenylsulfanyl)methyl)propyl)amino)benzenesulfonamide

[0931] This example was made by substituting EXAMPLE 90C and EXAMPLE 267B for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.37 (m, 1H), 8.01 (d, 1H), 7.57 (m, 2H), 7.35 (m, 10H), 7.19 (m, 4H), 6.72 (d, 2H), 6.64 (d, 1H), 3.72 (m, 1H), 3.36 (m, 2H), 3.13 (m, 5H), 2.99 (m, 1H), 2.92 (s, 3H), 1.92 (m, 1H), 1.58 (m, 3H), 1.31 (m, 2H), 0.98 (t, 3H).

EXAMPLE 269

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0932] This example was made by substituting EXAMPLE 267B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.42 (m, 1H), 8.03 (dd, 1H), 7.67 (m, 3H), 7.36 (m, 10H), 7.19 (m, 3H), 6.74 (d, 2H), 6.65 (d, 1H), 3.64 (m, 3H), 3.31 (m, 4H), 3.11 (s, 2H), 2.53 (m, 4H), 1.69 (m, 2H), 0.98 (t, 3H).

EXAMPLE 270A

[0933] This example was prepared by substituting (S)- 2-amino-4-methyl-pentan-1-ol for (S)-2-Amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 270B

[0934] This example was prepared by substituting EXAMPLE 270A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 270C

N-(4-(4-((9'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-methyl-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[0935] This example was made by substituting EXAMPLE 270B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H), 8.38 (d, 1H), 8.00 (dd, 1H), 7.63 (d, 2H), 7.49 (m, 1H), 7.35 (m, 8H), 7.22 (m, 4H), 6.79 (d, 2H), 6.60 (d, 1H), 3.85 (m, 1H), 3.42 (s, 2H), 3.28 (m, 4H), 3.09 (d, 2H), 2.47 (m, 4H), 1.73 (m, 3H), 0.96 (d, 3H), 0.86 (d, 3H).

EXAMPLE 271

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1S)-3-methyl-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[0936] This example was made by substituting EXAMPLE 90C and EXAMPLE 270B for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H), 8.36 (d, 2H), 7.98 (dd, 1H), 7.60 (d, 2H), 7.35 (m, 9H), 7.20 (m, 4H), 6.64 (m, 3H), 3.80 (m, 1H), 3.34 (s, 2H), 3.12 (s, 3H), 3.07 (m, 2H), 2.92 (m, 4H), 1.57 (m, 5H, 1.30 (m, 2H), 0.95 (d, 3H), 0.85 (d, 3H).

EXAMPLE 272A

[0937] 1-Tert-butoxycarbonylaminocyclopropane carboxylic acid (1.018 g) in THF (6 mL) at 0°C was treated with 1M borane·THF (15 mL), stirred at 25°C, treated with 3M NaOH, (5 mL), and extracted with diethyl ether. The extract was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 272B

[0938] This example was prepared by substituting EXAMPLE 272A for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 272C

[0939] 272B (0.090 g) in dichloromethane/TFA at 25°C was stirred for 16 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5% methanol/dichloromethane.

EXAMPLE 272 D

[0940] This example was prepared by substituting EXAMPLE 272C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 272E

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopropyl)amino)benzene-sulfonamide

[0941] This example was made by substituting EXAMPLE 272D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, 1H), 8.60 (s, 1H), 8.14 (dd, 1H), 7.63 (d, 2H), 7.49 (m, 1H), 7.35 (m, 6H), 7.25 (m, 3H), 7.06 (m, 3H), 6.80 (d, 2H), 3.41 (s, 2H), 3.28 (m, 4H), 3.22 (s, 2H), 2.47 (m, 4H), 1.01 (m, 4H).

EXAMPLE 273A

[0942] This example was prepared by substituting (1-hydroxymethyl-cyclohexyl)carbamic acid tert-butyl ester, prepared as described in Bioorg. Med. Chem. Lett., 2003; 13; 1883, for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 273B

[0943] This example was prepared by substituting EXAMPLE 273A for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 273C

[0944] This example was prepared by substituting EXAMPLE 273B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 273D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclohexyl)amino)benzene-sulfonamide

[0945] This example was made by substituting EXAMPLE 273C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.63 (s, 1H), 7.92 (d, 1H), 7.68 (m, 2H), 7.47 (m, 5H), 7.32 (m, 1H), 7.20 (m, 4H), 6.94 (m, 6H), 6.78 (m, 1H), 4.38 (s, 2H), 3.56 (m, 4H), 3.38 (s, 2H), 2.31 (m, 4H), 1.47 (m, 10H).

EXAMPLE 274A

[0946] This example was prepared by substituting (R)-2-amino-propan-1-ol for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 274B

[0947] This example was prepared by substituting EXAMPLE 274A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 274C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-methyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0948] This example was made by substituting EXAMPLE 274B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (br s, 1H), 8.42 (br s, 1H), 8.03 (d, 1H), 7.65 (d, 2H), 7.50 (m, 1H), 7.34 (m, 9H), 7.22 (m, 3H), 6.77 (d, 2H), 6.63 (m, 1H), 3.88 (m, 1H), 3.42 (s, 2H), 3.26 (m, 4H), 3.10 (d, 2H), 2.48 (m, 4H), 1.43 (d, 3H).

EXAMPLE 275A

[0949] This example was prepared by substituting (S)-2-amino-propan-1-ol for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 275B

[0950] This example was prepared by substituting EXAMPLE 275A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 275C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-9-(((1S)-1-methyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[0951] This example was made by substituting EXAMPLE 275B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, 1H), 8.45 (d, 1H), 8.04 (dd, 1H), 7.64 (d, 2H), 7.56 (m, 1H), 7.35 (m, 10H), 7.20 (m, 3H), 6.77 (d, 2H), 6.65 (d, 1H), 3.91 (m, 1H), 3.51 (s, 2H), 3.27 (t, 4H), 3.12 (m, 2H), 2.48 (t, 4H), 1.45 (d, 3H).

EXAMPLE 276A

[0952] This example was prepared by substituting (1R, 2R)-(2-hydroxycyclohexyl)carbamic acid tert-butyl ester, prepared as described in Synth.Commun. 1992, 22, 3003, for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

[0953] This example was prepared by substituting EXAMPLE 276A for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 276C

[0954] This example was prepared by substituting EXAMPLE 276B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 276D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R,2S)-2-(phenylsulfanyl)cyclohexyl)amino)benzenesulfonamide

[0955] This example was made by substituting EXAMPLE 276C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.78 (s, 1H), 8.07 (d, 1H), 7.61 (m, 3H), 7.35 (m, 10H), 7.09 (m, 3H), 6.76 (m, 3H), 3.84 (s, 1H), 3.65 (s, 1H), 3.48 (m, 2H), 3.25 (m, 4H), 2.47 (m, 4H), 1.73 (m, 8H).

EXAMPLE 277

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[0956] This example was made by substituting EXAMPLE 276C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.92 (d, 1H), 8.80 (d, 1H), 8.08 (dd, 1H), 7.66 (d, 2H), 7.53 (m, 1H), 7.35 (m, 8H), 7.23 (m, 1H), 7.11 (m, 3H), 6.78 (m, 3H), 3.87 (m, 1H), 3.65 (m, 1H), 3.46 (s, 2H), 3.28 (m, 4H), 2.49 (m, 4H), 1.75 (m, 8H).

EXAMPLE 278A

[0957] This example was prepared by substituting (1S,2R)-(2-hydroxycyclohexyl)carbamic acid tert-butyl ester, prepared as described in Eur. J. Org. Chem., 1998, 9, 1771, for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 278B

[0958] This example was prepared by substituting EXAMPLE 278A for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 278C

[0959] This example was prepared by substituting EXAMPLE 278B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 278D

4-(((1R)-5-amino-1-((phenylsulfanyl)methyl)pentyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0960] This example was made by substituting EXAMPLE 278C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, 1H), 8.80 (d, 1H), 8.09 (dd, 1H), 7.64 (d, 2H), 7.53 (m, 1H), 7.35 (m, 8H), 7.12 (m, 3H), 6.80 (m, 3H), 3.87 (m, 1H), 3.66 (m, 1H), 3.50 (s, 2H), 3.32 (m, 4H), 2.50 (m, 4H), 1.85 (m, 8H).

EXAMPLE 279A

[0961] This example was prepared by substituting S-(1-hydroxymethyl-2-pyridin-3-yl-ethyl)-carbamic acid tert-butyl ester for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 279B

[0962] This example was prepared by substituting EXAMPLE 279A for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 279C

[0963] This example was prepared by substituting EXAMPLE 279B for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 279D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethyl)amino)benzenesulfonamide

[0964] This example was made by substituting EXAMPLE 795333C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, 1H), 8.48 (m, 3H), 7.97 (dd, 1H), 7.64 (d, 2H), 7.53 (m, 2H), 7.37 (m, 9H), 7.23 (m, 5H), 6.75 (d, 2H), 6.53 (d, 1H), 4.00 (m, 1H), 3.50 (s, 2H), 3.26 (m, 5H), 3.13 (d, 2H), 2.98 (m, 1H), 2.48 (m, 4H).

EXAMPLE 280

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-(((1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethyl)amino)benzenesulfonamide

[0965] This example was made by substituting EXAMPLE 90C and EXAMPLE 279C for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.62 (s, 1H), 8.53 (s, 1H), 8.45 (d, 1H), 8.15 (d, 1H), 7.81 (d, 1H), 7.69 (m, 3H), 7.34 (m, 9H), 7.19 (m, 4H), 6.90 (d, 2H), 6.54 (d, 1H), 4.18 (m, 1H), 3.34 (m, 6H), 3.12 (s, 3H), 3.04 (m, 2H), 2.94 (s, 2H), 1.61 (m, 2H), 1.45 (m, 2H).

EXAMPLE 281

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S,2R)-2-(phenylsulfanyl)cyclohexyl)amino)benzenesulfonamide

[0966] This example was made by substituting EXAMPLE 278C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, 1H), 8.79 (d, 1H), 8.06 (dd, 1H), 7.69 (m, 3H), 7.41 (m, 8H), 7.24 (m, 1H), 7.11 (m, 3H), 6.80 (d, 1H), 6.74 (d, 2H), 3.86 (m, 1H), 3.66 (m, 1H), 3.29 (m, 8H), 2.52 (s, 2H), 2.07 (m, 1H), 1.81 (m, 5H), 1.51 (m, 2H).

EXAMPLE 282A

[0967] This example was prepared by substituting (1-amino-cyclopentyl)-methanol and bis(2-methyl-3-furyl)disulphide for (S)-2-amino-butan-1-ol and phenyl disulphide, respectively, in EXAMPLE 267A.

EXAMPLE 282B

[0968] This example was prepared by substituting EXAMPLE 282A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 282C

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((1-(((2-methyl-3-furyl)sulfanyl)methyl)cyclopentyl)amino)-3-nitrobenzenesulfonamide

[0969] This example was made by substituting EXAMPLE 282B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, 1H), 8.68 (s, 1H), 8.06 (dd, 1H), 7.65 (d, 2H), 7.53 (m, 1H), 7.33 (m, 7H), 6.91 (m, 1H), 6.88 (s, 1H), 6.78 (d, 2H), 5.99 (d, 1H), 3.47 (s, 2H), 3.26 (m, 4H), 3.18 (s, 2H), 2.46 (m, 4H), 2.14 (br s, 3H), 2.08 (m, 4H), 1.78 (m, 4H).

EXAMPLE 283

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1-(((2-methyl-3-furyl)sulfanyl)methyl)cyclopentyl)amino)-3-nitrobenzenesulfonamide

[0970] This example was made by substituting EXAMPLE 282B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, 1H), 8.68 (s, 1H), 8.07 (dd, 1H), 7.65 (d, 2H), 7.49 (m, 1H), 7.34 (m, 6H), 7.23 (m, 1H), 6.90 (m, 2H), 6.79 (d, 2H), 6.00 (d, 1H), 3.41 (s, 2H), 3.26 (m, 4H), 3.18 (s, 2H), 2.46 (m, 4H), 2.14 (s, 3H), 2.08 (m, 4H), 1.78 (m, 4H).

EXAMPLE 284

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1S)-2-(phenylsulfanyl)-1-(pyridin-3-ylmethyl)ethyl)amino)benzenesulfonamide

[0971] This example was made by substituting EXAMPLE 279C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (d, 1H), 8.50 (m, 3H), 7.98 (dd, 1H), 7.62 (d, 2H), 7.50 (m, 2H), 7.35 (m, 8H), 7.21 (m, 4H), 6.78 (d, 2H), 6.53 (d, 1H), 4.01 (m, 1H), 3.42 (s, 2H), 3.27 (m, 5H), 3.13 (d, 2H), 2.99 (m, 1H), 2.48 (m, 4H).

EXAMPLE 285A

[0972] This example was made by substituting 2-bromo-3-bromomethylpyridine, prepared as described in J. Am. Chem. Soc, 1985, 107, 7487, for 2-bromobenzyl bromide in EXAMPLE 2A.

EXAMPLE 285B

[0973] This example was made by substituting EXAMPLE 285A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 285C

[0974] This example was made by substituting EXAMPLE 285B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 285D

N-(4-(4-((2-(4-chlorophenyl)-3-pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0975] This example was made by substituting EXAMPLE 285C for EXAMPLE 1C in EXAMPLE 1D. ^{1}H NMR (300

MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.70 (m, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 8.11 (m, 1H), 7.86 (dd, 1H), 7.76 (d, 2H), 7.58 (m, 5H), 7.16 (m, 6H), 6. 94 (d, 2H), 4.19 (m, 1H), 3.54 (m, 4H), 3.39 (d, 2H), 3.13 (m, 4H), 2.75 (s, 3H), 2.74 (s, 3H), 2.49 (m, 4H), 2.14 (m, 2H).

EXAMPLE 286

N-(4-(4-((2-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0976] This example was made by substituting EXAMPLE 285C and 3-nitro-4-(2-phenylsulfanylethylamino)benzenesulfonamide, prepared as described in WO02/24636,
For EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, 1H), 8.78 (d, 1H), 8.67 (t, 1H), 8.34 (d, 1H), 8.10 (dd, 1H), 7.67 (d, 1H), 7.52 (m, 3H), 7.41 (m, 4H), 7.30 (m, 2H), 7.23 (m, 1H), 6.82 (d, 1H), 6.73 (d, 2H), 4.35 (s, 2H), 3.57 (q, 2H), 3.47 (m, 4H), 3.20 (t, 2H), 2.97 (m, 4H).

EXAMPLE 287

N-(4-(4-((2-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0977] This example was made by substituting EXAMPLE 285C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (d, 1H), 8.55 (d, 1H), 8.30 (d, 1H), 8.12 (m, 1H), 7.87 (dd, 1H), 7.76 (d, 2H), 7.57 (m, 5H), 7.16 (m, 6H), 6.94 (d, 2H), 4.19 (m, 1H), 3.97 (d, 2H), 3.58 (m, 7H), 3.38 (m, 5H), 3.19 (m, 4H), 3.01 (m, 4H), 2.17 (m, 2H).

EXAMPLE 288A

[0978] This example was made by substituting phenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 288B

[0979] This example was made by EXAMPLE 288A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 288C

3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[0980] This example was made by substituting EXAMPLE 288B and 3-nitro-4-(2-phenylsulfanylethylamino)-benzenesulfonamide, prepared as described in WO02/24636, for EXAMPLE 1C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 1D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (d, 1H), 8.65 (m, 2H), 8.14 (dd, 1H), 7.91 (m, 1H), 7.60 (m, 4H), 7.43 (m, 5H), 7.28 (m, 4H), 6.80 (m, 3H), 3.56 (m, 4H), 3.31 (m, 4H), 3.21 (t, 2H), 2.51 (m, 4H).

EXAMPLE 289

4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0981] This example was made by substituting EXAMPLE. 2888 and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.67 (d, 1H), 8.49 (dd, 1H), 8.07 (dd, 1H), 7.88 (dd, 1H), 7.78 (d, 2H), 7.48 (m, 6H), 7.26 (m, 2H), 7.12 (m, 3H), 6.95 (d, 1H), 6.88 (d, 2H), 4.14 (m, 1H), 3.66 (m, 4H), 3.53 (m, 2H), 3.25 (m, 6H), 2.51 (m, 10H),

2.13 (m, 1H), 1.92 (m, 1H).

EXAMPLE 290

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-((2-phenylpyridin-3-yl)methyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[0982] This example was made by substituting EXAMPLE 288B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (dd, 1H), 8.44 (d, 1H), 8.31 (d, 1H), 7.94 (dd, 1H), 7.79 (dd, 1H), 7.72 (d, 2H), 7.62 (m, 2H), 7.43 (m, 5H), 7.32 (m, 2H), 7.25 (m, 2H), 7.17 (m, 1H), 6.87 (d, 1H), 6.79 (d, 2H), 4.05 (m, 1H), 3.50 (s, 2H), 3.30 (m, 2H), 3.16 (s, 4H), 2.43 (m, 4H), 2.35 (m, 6H), 2.01 (m, 1H), 1.91 (m, 1H).

EXAMPLE 291A

[0983] This example was made by substituting 4-(methylsulfanyl)phenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 291B

[0984] This example was made by substituting EXAMPLE 291A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 291C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfanyl)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0985] This example was made by substituting EXAMPLE 291B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (dd, 1H), 8.67 (d, 1H), 8.42 (dd, 1H), 7.93 (dd, 1H), 7.74 (m, 3H), 7.50 (d, 2H), 7.44 (d, 2H), 7.22 (m, 2H), 7.04 (m, 4H), 6.94 (d, 2H), 4.36 (s, 2H), 4.17 (m, 1H), 3.43 (m, 5H), 3.24 (m, 3H), 3.04 (t, 4H), 2.87 (s, 6H), 2.51 (s, 3H), 2.24 (m, 2H).

EXAMPLE 292A

[0986] This example was made by substituting 4-methoxyphenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 292B

[0987] This example was made by substituting EXAMPLE 292A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 292C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-methoxyphenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0988] This example was made by substituting EXAMPLE 292B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.55 (dd, 1H), 8.45 (d, 1H), 8.33 (d, 1H), 7.91 (dd, 1H), 7.78 (dd, 1H), 7.73 (d, 2H), 7.63 (d, 2H), 7.33 (m, 3H), 7.21 (m, 3H), 7.01 (d, 2H), 6.86 (d, 1H), 6.80 (d, 2H), 4.04 (m, 1H), 3.79 (s, 3H), 3.50 (s, 2H), 3.18 (s, 4H), 3.00 (d, 2H), 2.68 (m, 2H), 2.45 (m, 4H), 2.33 (s, 6H), 1.95 (m, 2H).

EXAMPLE 293A

[0989] This example was made by substituting 4-dimethylaminophenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 293B

[0990] This example was made by substituting EXAMPLE 293A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 293

N-(4-(4-((2-(4-(dimethylamino)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[0991] This example was made by substituting EXAMPLE 293B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.66 (d, 1H), 8.46 (dd, 1H), 8.08 (dd, 1H), 7.94 (dd, 1H), 7.75 (d, 2H), 7.42 (m, 3H), 7.24 (m, 2H), 7.08 (m, 3H), 6.96 (d, 1H), 6.91 (d, 2H), 6.84 (d, 2H), 4.14 (m, 1H), 3.64 (s, 2H), 3.38 (m, 4H), 3.23 (m, 4H), 3.00 (s, 6H), 2.86 (s, 7H), 2.54 (m, 4H), 2.22 (m, 2H).

EXAMPLE 294A

[0992] This example was made by substituting 4-fluorophenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 294B

[0993] This example was made by substituting EXAMPLE 294A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 294

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-fluorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0994] This example was made by substituting EXAMPLE 294B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, CD_3OD) δ 8.74 (dd, 1H), 8.67 (d, 1H), 8.37 (dd, 1H), 7.93 (dd, 1H), 7.73 (m, 3H), 7.60 (m, 2H), 7.31 (m, 2H), 7.22 (m, 2H), 7.03 (m, 4H), 6.95 (d, 2H), 4.39 (s, 2H), 4.17 (m, 1H), 3.47 (m, 4H), 3.38 (m, 1H), 3.23 (m, 3H), 3.08 (m, 4H), 2.86 (s, 6H), 2.24 (m, 2H).

EXAMPLE 295A

[0995] This example was made by substituting 4-(methanesulphonyl)phenylboronic acid and EXAMPLE 285A for 4-chlorophenylboronic acid and EXAMPLE 2A, respectively, in EXAMPLE 2B.

EXAMPLE 295B

[0996] This example was made by substituting EXAMPLE 295A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 295C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfonyl)phenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[0997] This example was made by substituting EXAMPLE 295B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (m, 3H), 8.02 (d, 2H), 7.89 (m, 3H), 7.80 (m, 3H), 7.32 (m, 3H), 7.19 (m, 3H), 6.73 (m, 3H), 4.06 (m, 1H), 3.46 (s, 2H), 3.24 (m, 4H), 3.12 (d, 2H), 2.85 (m, 3H), 2.59 (s, 6H), 2.51 (m, 5H), 2.19 (m, 1H), 2.08 (m, 1H).

EXAMPLE 205A

[0998] This example was made by substituting 2-bromoethylamine hydrobromide for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 296A

[0999] This example was made by substituting pyridin-4-yl-methanethiol for 2-mercaptoimidazole in EXAMPLE 205B.

EXAMPLE 296B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(pyridin-4-ylsulfanyl)ethyl)amino)benzenesulfonamide

[1000] This example was made by substituting 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, 1H), 8.62 (m, 1H), 8.42 (d, 2H), 8.19 (dd, 1H), 7.62 (d, 3H), 7.35 (m, 7H), 7.15 (d, 2H), 6.92 (d, 1H), 6.77 (d, 2H), 3.70 (q, 2H), 3.54 (s, 2H), 3.32 (m, 6H), 2.53 (m, 4H).

EXAMPLE 297A

[1001] This example was made by substituting 4-(methanesulphonyl)phenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 297B

[1002] This example was made by substituting EXAMPLE 297A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 297C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(methylsulfonyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1003] This example was made by substituting EXAMPLE 297B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (d, 1H), 8.57 (d, 1H), 7.96 (d, 2H), 7.80 (m, 3H), 7.66 (d, 2H), 7.49 (m, 1H), 7.38 (m, 2H), 7.29 (m, 2H), 7.19 (m, 4H), 6.71 (m, 3H), 4.04 (m, 1H), 3.38 (s, 2H), 3.18 (m, 4H), 3.10 (m, 6H), 2.85 (m, 2H), 2.58 (s, 6H), 2.45 (m, 4H), 2.20 (m, 1H), 2.07 (m, 1H).

EXAMPLE 298

N-(4-(4-((4'-(methylsulfonyl)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1004] This example was made by substituting EXAMPLE 297B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.29 (d, 1H), 8.01 (d, 2H), 7.87 (dd, 1H), 7.76 (d, 2H), 7.67 (d, 2H), 7.55 (m, 2H), 7.37 (d, 1H), 7.23 (m, 2H), 7.15 (m, 4H), 6.93 (s, 2H), 4.19 (m, 1H), 3.95 (s, 2H), 3.54 (m, 12H), 3.40 (d, 2H), 3.26 (s, 3H), 3.19 (m, 4H), 3.02 (m, 2H), 2.17 (m, 2H).

EXAMPLE 299A

[1005] EXAMPLE 19C (0.938 g) in dichloromethane (10 mL) at 25°C was treated with di(tert-butyl) dicarbonate (0.873 g), stirred for 24 hours, and concentrated. The concentrate was flash chromatographed on silica gel with 20-60% ethyl acetate/hexanes.

EXAMPLE 299B

[1006] This example was prepared by substituting EXAMPLE 299A for EXAMPLE 67A in EXAMPLE 67B.

EXAMPLE 299C

[1007] This example was prepared by substituting EXAMPLE 299B for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 299D

[1008] This example was prepared by substituting EXAMPLE 299C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 299E

[1009] EXAMPLE 299D (0.485 g) at 25°C was treated with 1M borane·THF (8 mL), stirred for 16 hours, treated with methanol (5 mL), and concentrated. The concentrate was refluxed in methanol/12M HCl (30 mL/6 mL) for 8 hours and concentrated. The concentrate was flash chromatographed on silica gel with 1-20% methanol/NH_3-saturated dichloromethane.

EXAMPLE 299F

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfonyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1010] This example was prepared by substituting EXAMPLE 299E for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (d, 1H), 8.41 (d, 1H), 8.07 (dd, 1H), 7.77 (d, 2H), 7.63 (dd, 3H), 7.46 (m, 3H), 7.34 (m, 6H), 7.24 (m, 1H), 7.00 (d, 1H), 6.78 (d, 2H), 4.54 (m, 1H), 3.69 (m, 4H), 3.45 (d, 2H), 3.41 (s, 2H), 3.26 (m, 4H), 2.47 (m, 6H), 2.34 (m, 3H), 2.20 (m, 2H), 1.86 (m, 2H).

EXAMPLE 300A

[1011] This example was made by substituting 4-dimethylaminophenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 300B

[1012] This example was made by substituting EXAMPLE 300A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 300C

N-(4-(4-((4'-(dimethylamino)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1013] This example was made by substituting EXAMPLE 300B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.20 (d, 1H), 7.81 (dd, 1H), 7.72 (m, 2H), 7.50 (m, 1H), 7.30 (m, 6H), 7.24 (m, 4H), 6.90 (d, 1H), 6.79 (m, 4H), 4.07 (m, 1H), 3.43 (s, 2H), 3.21 (m, 8H), 2.92 (s, 6H), 2.56 (s, 6H), 2.43 (m, 4H), 2.05 (m, 2H).

EXAMPLE 301A

[1014] This example was prepared by substituting EXAMPLE 18C for EXAMPLE 19C in EXAMPLE 299A.

EXAMPLE 301B

[1015] This example was prepared by substituting EXAMPLE 301A for EXAMPLE 67A in EXAMPLE 67B.

EXAMPLE 301C

[1016] This example was prepared by substituting EXAMPLE 301B for EXAMPLE 272B in EXAMPLE 272C.

EXAMPLE 301D

[1017] This example was prepared by substituting EXAMPLE 301C for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 301E

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(phenylsulfonyl)butanamide

[1018] This example was made by substituting EXAMPLE 301D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (m, 2H), 7.90

(dd, 1H), 7.76 (d, 2H), 7.58 (dd, 2H), 7.50 (m, 6H), 7.38 (m, 4H), 7.23 (m, 2H), 6.90 (d, 2H), 4.70 (m, 1H), 4.17 (m, 1H), 3.76 (m, 1H), 3.43 (s, 2H), 3.25 (m, 4H), 2.94 (m, 1H), 2.88 (s, 3H), 2.77 (m, 4H), 2.42 (m, 4H).

EXAMPLE 302A

[1019] This example was prepared by substituting 3-amino-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester, prepared as described in J. Org. Chem., 1997, 62, 4197, for (S)-2-amino-butan-1-ol in EXAMPLE 267A.

EXAMPLE 302B

[1020] This example was made by substituting EXAMPLE 302A for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 302C

[1021] This example was made by substituting EXAMPLE 302B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 302D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((3S,4R)-(phenylsulfanyl)pyrrolidin-4-yl)amino)benzenesulfonamide

[1022] This example was prepared by substituting EXAMPLE 302C for EXAMPLE 272B in EXAMPLE 272C. ^{1}H NMR (300 MHz, CD_3OD) δ 8.78 (d, 1H), 7.94 (dd, 1H), 7.74 (m, 3H), 7.55 (m, 7H), 7.36 (m, 7H), 6.96 (d, 2H), 6.75 (d, 1H), 4.51 (m, 1H), 4.44 (s, 2H), 4.02 (m, 2H), 3.86 (q, 1H), 3.49 (m, 2H), 3.43 (m, 2H), 3.35 (m, 2H), 3.14 (m, 4H).

EXAMPLE 303

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-4-ylsulfanyl)propyl)amino)benzenesulfonamide

[1023] This example was made by substituting pyridine-4-thiol for isopropylamine in EXAMPLE 35B. ^{1}H NMR (400 MHz, CD_3OD) δ 8.64 (m, 1H), 8.23 (m, 2H), 7.83 (m, 3H), 7.50 (m, 1H), 7.36 (m, 7H), 7.23 (m, 5H), 7.11 (m, 3H), 6.85 (d, 2H), 6.78 (d, 1H), 4.14 (m, 1H), 3.60 (m, 1H), 3.47 (s, 2H), 3.21 (m, 6H), 3.10 (m, 1H), 2.46 (m, 4H), 2.26 (m, 1H), 2.12 (m, 1H).

EXAMPLE 304A

[1024] A mixture of 3-bromo-4-methylpyridine (1.34 g) and NCS (1.43 g) in CCl_4 (10 mL) at reflux was stirred for 21 hours and filtered. The filtrate was dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 0-30% ethyl acetate/hexanes.

EXAMPLE 304B

[1025] This example was prepared by substituting EXAMPLE 304A for 2-bromobenzyl bromide in EXAMPLE 2A.

EXAMPLE 304C

[1026] This example was prepared by substituting EXAMPLE 304B for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 304D

[1027] This example was prepared by substituting EXAMPLE 304C for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 304E

N-(4-(4-((3-(4-chlorophenyl)pyridin-4-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1028] This example was prepared by substituting EXAMPLE 304D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (d, 1H), 9.33 (d, 1H), 8.69 (d, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.75 (m, 3H), 7.57 (d, 2H), 7.48 (d, 2H), 7.17 (m, 6H), 6.94 (d, 2H), 4.18 (m, 1H), 3.39 (d, 2H), 3.13 (m, 4H), 2.75 (m, 3H), 2.73 (m, 3H), 2.14 (m, 2H).

EXAMPLE 305

N-(4-(4-((3-(4-chlorophenyl)pyridin-4-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1029] This example was prepared by substituting EXAMPLE 304D and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, 1H), 8.75 (d, 1H), 8.66 (m, 2H), 8.11 (dd, 1H), 8.08 (d, 1H), 7.66 (d, 2H), 7.51 (d, 2H), 7.40 (d, 2H), 7.27 (m, 5H), 6.81 (d, 1H), 6.78 (d, 2H), 3.90 (s, 2H), 3.57 (m, 2H), 3.42 (m, 4H), 3.20 (t, 2H), 2.75 (m, 4H).

EXAMPLE 306A

[1030] 2-Bromo-cyclopent-1-enecarbaldehyde, prepared as described in Collect. Czech. Chem. Commun., 1961, 26, 3059-3073, (1.5 g), 4-piperazin-1-yl-benzoic acid ethyl ester (2 g) in ethanol (10 mL) at 25°C was treated with sodium cyanoborohydride (0.36 g), pH was adjusted to 5-6 with acetic acid, stirred for 18 hours, filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5-10% ethyl acetate/hexanes.

EXAMPLE 306B

[1031] This example was made by substituting EXAMPLE 306A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 306C

[1032] This example was made by substituting EXAMPLE 306B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 306D

N-(4-(4-((2-(4-chlorophenyl)-1-cyclopenten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1033] This example was prepared by substituting EXAMPLE 306C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (m, 1H), 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.32 (d, 2H), 7.28 (d, 2H), 7.22 (d, 2H), 7.14 (m, 4H), 6.97 (d, 2H), 4.18 (m, 1H), 3.90 (m, 4H), 3.54 (m, 4H), 3.39 (d, 2H), 3.14 (m, 4H), 2.92 (m, 2H), 2.76 (s, 6H), 2.64 (m, 2H), 2.15 (m, 2H), 1.96 (m, 2H).

EXAMPLE 307A

[1034] This example was prepared by substituting 2-bromo-cyclohex-1-enecarbaldehyde, prepared as described in Collect. Czech. Chem. Commun., 1961, 26, 3059, for 2-bromo-cyclopent-1-enecarbaldehyde in EXAMPLE 306A.

EXAMPLE 307B

[1035] This example was made by substituting EXAMPLE 307A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 307C

[1036] This example was made by substituting EXAMPLE 307B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 307D

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1037] This example was made by substituting EXAMPLE 307C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, 1H), 8.03 (d, 1H), 7.61 (dd, 1H), 7.53 (d, 2H), 7.15 (d, 2H), 6.97 (m, 2H), 6.89 (m, 6H), 6.70 (d, 2H), 3.93 (m, 1H), 3.37 (m, 4H), 3.13 (m, 4H), 2.89 (m, 4H), 2.49 (s, 6H), 2.24 (s, 2H), 1.98 (d, 4H), 1.89 (q, 2H), 1.43 (m, 4H).

EXAMPLE 308A

[1038] This example was made by substituting EXAMPLE 306A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 308B

N-(4-(4-((2-bromo-1-cyclopenten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1039] This example was made by substituting EXAMPLE 308A for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.50 (d, 1H), 8.25 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.17 (m, 3H), 7.09 (m, 4H), 6.98 (d, 2H), 4.14 (m, 1H), 3.80 (s, 2H), 3.35 (d, 2H), 3.28 (m, 4H), 3.11 (m, 4H), 2.70 (s, 6H), 2.64 (m, 2H), 2.41 (m, 2H), 2.10 (q, 2H), 1.93 (m, 2H).

EXAMPLE 309

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1040] This example was made by substituting EXAMPLE 307C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.50 (d, 1H), 8.37 (d, 1H), 7.80 (dd, 1H), 7.72 (d, 2H), 7.37 (d, 2H), 7.28 (m, 2H), 7.17 (m, 5H), 7.04 (d, 1H), 6.85 (d, 2H), 4.14 (s, 1H), 3.53 (m, 4H), 3.36 (m, 4H), 3.21 (m, 4H), 2.80 (s, 2H), 2.45 (m, 2H), 2.34 (m, 5H), 2.19 (m, 5H), 2.01 (m, 1H), 1.87 (m, 1H), 1.67 (m, 4H).

EXAMPLE 310

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1041] This example was made by substituting EXAMPLE 307C and EXAMPLE 18F for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.80 (d, 1H), 7.63 (m, 3H), 7.24 (m, 6H), 7.12 (m, 1H), 7.02 (d, 2H), 6.70 (d, 2H), 6.58 (d, 1H), 5.74 (s, 1H), 3.76 (m, 1H), 3.16 (m, 6H), 3.07 (m, 4H), 2.90 (m, 2H), 2.68 (s, 2H), 2.41 (m, 2H), 2.19 (m, 4H), 2.10 (m, 4H), 1.95 (m, 2H), 1.57 (m, 4H).

EXAMPLE 311A

[1042] This example was made by substituting EXAMPLE 307A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 311B

N-(4-(4-((2-bromo-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1043] This example was made by substituting EXAMPLE 311A for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.81 (d, 2H), 7.21 (m, 3H), 7.12 (m, 3H), 7.03 (d, 2H), 4.19

(m, 1H), 3.89 (s, 2H), 3.30 (m, 8H), 3.15 (m, 4H), 2.74 (s, 6H), 2.56 (m, 2H), 2.25 (m, 2H), 2.15 (q, 2H), 1.68 (m, 4H).

EXAMPLE 312A

[1044] A mixture of DMF (10 mL) and chloroform (200 mL) at 5°C-was treated with PBr_3 (10 mL), stirred at 25°C for 40 minutes, treated with tetrahydropyran-4-one (5 g) in chloroform (50 mL) at 0°C, stirred at 25°C for 18 hours, poured onto ice, treated with sodium bicarbonate, and extracted with diethyl ether. The extract was washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$), filtered and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 312B

[1045] This example was prepared by substituting 312A for 2-bromo-cyclopent-1-enecarbaldehyde in EXAMPLE 306A.

EXAMPLE 312C

[1046] This example was made by substituting EXAMPLE 312B for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 312D

[1047] This example was made by substituting EXAMPLE 312C for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 312E

N-(4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1048] This example was made by substituting EXAMPLE 312D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.29 (d, 1H), 8.03 (d, 1H), 7.61 (dd, 1H), 7.52 (d, 2H), 7.19 (d, 2H), 6.98 (m, 4H), 6.89 (m, 4H), 6.70 (d, 2H), 3.99 (s, 2H), 3.93 (m, 1H), 3.69 (s, 2H), 3.58 (t, 2H), 3.13 (s, 8H), 2.88 (m, 4H), 2.49 (s, 6H), 2.12 (m, 2H), 1.89 (q, 2H).

EXAMPLE 313A

[1049] This example was made by substituting EXAMPLE 312B and 4-methoxyphenylboronic acid for EXAMPLE 2A and 4-chlorophenylboronic acid, respectively, in EXAMPLE 2B.

EXAMPLE 313B

[1050] This example was made by substituting EXAMPLE 313A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 313

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-methoxyphenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1051] This example was made by substituting EXAMPLE 313B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.28 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.23 (m, 2H), 7.14 (m, 4H), 7.05 (d, 2H), 6.95 (d, 2H), 6.91 (d, 2H), 4.19 (m, 1H), 3.86 (m, 2H), 3.73 (s, 3H), 3.60 (m, 4H), 3.39 (d, 2H), 3.15 (m, 4H), 2.74 (m, 8H), 2.26 (s, 2H), 2.20 (s, 2H), 2.15 (q, 2H), 1.70 (s, 4H).

EXAMPLE 314A

[1052] This example was made by substituting EXAMPLE 312B and 4-fluorophenylboronic acid for EXAMPLE 2A and 4-chlorophenylboronic acid, respectively, in EXAMPLE 2B.

EXAMPLE 313B

[1053] This example was made by substituting EXAMPLE 314A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 314C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-fluorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1054] This example was made by substituting EXAMPLE 313B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.79 (d, 2H), 7.23 (m, 2H), 7.15 (m, 8H), 6.96 (d, 2H), 4.19 (m, 1H), 3.86 (m, 4H), 3.60 (s, 2H), 3.39 (d, 2H), 3.15 (m, 4H), 2.77 (m, 8H), 2.27 (s, 2H), 2.22 (s, 2H), 2.15 (q, 2H), 1.72 (s, 4H).

EXAMPLE 315A

[1055] This example was made by substituting EXAMPLE 307A and phenylboronic acid for EXAMPLE 2A and 4-chlorophenylboronic acid, respectively, in EXAMPLE 2B.

EXAMPLE 315B

[1056] This example was made by substituting EXAMPLE 315A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 315C

[1057] This example was made by substituting EXAMPLE 315B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.36 (m, 2H), 7.28 (m, 1H), 7.21 (m, 2H), 7.13 (m, 6H), 6.95 (d, 2H), 4.19 (s, 1H), 3.87 (s, 2H), 3.62 (m, 4H), 3.39 (d, 2H), 3.15 (m, 4H), 2.74 (m, 8H), 2.29 (s, 2H), 2.22 (s, 2H), 2.14 (q, 2H), 1.72 (m, 4H).

EXAMPLE 316A

[1058] This example was prepared by substituting 2-bromo-cyclooct-1-enecarbaldehyde for 2-bromo-cyclopent-1-enecarbaldehyde in EXAMPLE 306A.

EXAMPLE 316B

[1059] This example was made by substituting EXAMPLE 316A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 316C

[1060] This example was made by substituting EXAMPLE 316B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 316D

N-(4-(4-((2-(4-chlorophenyl)-1-cycloocten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1061] This example was made by substituting EXAMPLE 316C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.30 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.43 (d, 2H), 7.17 (m, 8H), 6.95 (d, 2H), 4.19 (m, 5H), 3.89 (m, 2H), 3.64 (s, 2H), 3.39 (m, 4H), 3.13 (m, 4H), 2.75 (s, 3H), 2.74 (s, 3H), 2.46 (m, 2H), 2.14 (q, 2H), 1.66 (m, 2H), 1.54 (m, 4H), 1.41 (m, 2H).

EXAMPLE 317A

[1062] This example was made by substituting EXAMPLE 312B and 4-methylthiophenylboronic acid for EXAMPLE 2A and 4-chlorophenylboronic acid, respectively, in EXAMPLE 2B.

EXAMPLE 317B

[1063] This example was made by substituting EXAMPLE 317A for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 317C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2-(4-(methylsulfanyl)phenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1064] This example was made by substituting EXAMPLE 317B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.79 (d, 2H), 7.22 (m, 4H), 7.11 (m, 6H), 6.95 (d, 2H), 4.17 (m, 1H), 3.90 (m, 4H), 3.65 (m, 4H), 3.39 (d, 2H), 3.12 (m, 4H), 2.75 (s, 3H), 2.74 (s, 3H), 2.45 (s, 3H), 2.24 (m, 4H), 2.14 (q, 2H), 1.71 (m, 4H).

EXAMPLE 318A

[1065] This example was prepared by substituting 2-bromo-cyclohept-1-enecarbaldehyde for 2-bromo-cyclopent-1-enecarbaldehyde in EXAMPLE 306A.

EXAMPLE 318B

[1066] This example was made by substituting EXAMPLE 318A for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 318C

[1067] This example was made by substituting EXAMPLE 318B for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 318D

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1068] This example was made by substituting EXAMPLE 318C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.29 (d, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.40 (d, 2H), 7.22 (m, 2H), 7.14 (m, 6H), 6.95 (d, 2H), 4.19 (m, 1H), 3.87 (s, 2H), 3.61 (m, 2H), 3.39 (m, 4H), 3.15 (m, 4H), 2.75 (m, 8H), 2.46 (m, 4H), 2.14 (m, 2H), 1.80 (m, 2H), 1.56 (m, 4H).

EXAMPLE 319

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1069] This example was made by substituting EXAMPLE 318C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.55 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.40 (d, 2H), 7.22 (m, 3H), 7.14 (m, 6H), 6.93 (d, 2H), 4.20 (m, 1H), 3.91 (m, 4H), 3.39 (m, 6H), 3.18 (m, 6H), 3.03 (m, 2H), 2.79 (m, 2H), 2.45 (m, 4H), 2.16 (q, 2H), 1.81 (m, 2H), 1.56 (m, 4H).

EXAMPLE 320A

[1070] This example was made by substituting 4,4-dimethyl-cyclohexanone for tetrahydro-pyran-4-one in EXAMPLE 312A.

EXAMPLE 320B

[1071] This example was prepared by substituting 320A for 2-bromo-cyclopent-1-enecarbaldehyde in EXAMPLE 306A.

EXAMPLE 320C

[1072] This example was made by substituting EXAMPLE 320B for EXAMPLE 2A in EXAMPLE 2B.

EXAMPLE 320D

[1073] This example was made by substituting EXAMPLE 320C for EXAMPLE 2B in EXAMPLE 2C.

EXAMPLE 320E

N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1074] This example was made by substituting EXAMPLE 320D for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.28 (d, 1H), 7.86 (dd, 1H), 7.79 (d, 2H), 7.41 (m, 2H), 7.23 (m, 2H), 7.14 (m, 6H), 6.95 (d, 2H), 4.19 (m, 1H), 3.90 (m, 1H), 3.39 (d, 2H), 3.15 (s, 6H), 2.74 (m, 8H), 2.54 (m, 3H), 2.28 (m, 2H), 2.14 (q, 2H), 2.03 (s, 2H), 1.47 (t, 2H), 0.98 (s, 6H).

EXAMPLE 321

N-(4-(4-((2-(4-chlorophenyl)-5,5-dimethyl-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1075] This example was made by substituting EXAMPLE 320D and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, 1H), 8.29 (d, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.41 (m, 2H), 7.22 (m, 2H), 7.14 (m, 6H), 6.95 (d, 2H), 4.20 (m, 1H), 3.93 (m, 2H), 3.57 (m, 4H), 3.39 (m, 6H), 3.19 (m, 4H), 3.02 (m, 2H), 2.81 (m, 2H), 2.53 (s, 2H), 2.27 (m, 2H), 2.17 (q, 2H), 2.01 (s, 2H), 1.47 (t, 2H), 0.98 (s, 6H).

EXAMPLE 322A

[1076] A mixture of EXAMPLE 32A (1 g) and 60% oily sodium hydride (0.30 g) in toluene (15 mL) was refluxed for 1 hour, treated with 4-(2-chloroethyl)morpholine (2 g), refluxed for 18 hours, treated with aqueous NH_4Cl and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5-15% 7M NH_3 in methanol/dichloromethane.

EXAMPLE 322B

[1077] This example was made by substituting EXAMPLE 322A and phenylboronic acid for EXAMPLE 32B and 4-chlorophenylboronic acid, respectively, in EXAMPLE 32C.

EXAMPLE 322C

[1078] This example was made by substituting EXAMPLE 322B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 322D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(morpholin-4-yl)ethoxy)piperidin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1079] This example was made by substituting EXAMPLE 322C and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 11.08 (m, 1H), 10.02 (m, 1H), 8.30 (s, 1H), 8.28 (d, 1H), 7.98 (t, 2H), 7.61 (dd, 1H), 7.50 (d, 2H), 7.11 (m, 8H), 6.75 (m, 5H), 6.63 (d, 1H), 3.67 (m, 6H), 3.12 (m, 4H), 2.79 (m, 10H), 1.52 (m, 4H), 1.34 (s, 6H).

EXAMPLE 323

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(morpholin-4-yl)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1080] This example was made by substituting EXAMPLE 322C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 11.16 (m, 1H), 10.08 (m, 1H), 8.53 (t, 1H), 8.36 (d, 1H), 7.68 (dd, 1H), 7.47 (d, 2H), 7.07 (m, 16H), 6.62 (d, 1H), 3.55 (m, 4H), 3.45 (m, 4H), 2.95 (m, 12H), 1.52 (m, 2H), 1.26 (m, 2H), 1.00 (m, 2H).

EXAMPLE 324A

[1081] This example was made by substituting 1-(2-chloroethyl)pyrrolidine for 4-(2-chloroethyl)morpholine in EXAMPLE 322A.

EXAMPLE 324B

[1082] This example was made by substituting EXAMPLE 324A and phenylboronic acid for EXAMPLE 32B and 4-chlorophenylboronic acid, respectively, in EXAMPLE 32C.

EXAMPLE 324C

[1083] This example was made by substituting EXAMPLE 324B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 324D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1084] This example was made by substituting EXAMPLE 324C and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (s, 1H), 10.39 (m, 1H), 8.50 (d, 2H), 7.82 (dd, 1H), 7.71 (d, 2H), 7.33 (m, 10H), 7.16 (dd, 1H), 6.99 (t, 2H), 6.91 (t, 1H), 6.82 (d, 2H), 3.62 (m, 2H), 3.38 (m, 6H), 3.28 (m, 2H), 2.96 (m, 6H), 1.93 (m, 2H), 1.82 (m, 2H), 1.55 (s, 6H), 1.48 (m, 2H), 1.20 (m, 2H).

EXAMPLE 325

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1085] This example was made by substituting EXAMPLE 324C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6).δ 11.95 (s, 1H), 10.46 (m, 1H), 8.74 (t, 1H), 8.58 (d, 1H), 7.90 (m, 1H), 7.67 (d, 2H), 7.28 (m, 14H), 6.81 (d, 2H), 3.66 (m, 2H), 3.38 (m, 6H), 3.27 (m, 4H), 2.98 (m, 6H), 1.93 (m, 2H), 1.82 (m, 2H), 1.48 (m, 2H), 1.19 (m, 2H).

EXAMPLE 326

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(pyrrolidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[1086] This example was made by substituting EXAMPLE 324C and EXAMPLE 264B for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR 500 MHz, DMSO-d_6) δ 11.97 (s, 1H), 10.65 (m, 1H), 8.47 (s, 1H), 8.41 (d, 1H), 7.82 (dd, 1H), 7.73 (d, 2H), 7.27 (m, 10H), 6.81 (m, 6H), 3.63 (m, 2H), 3.35 (m, 6H), 2.96 (m, 6H), 1.90 (m, 12H), 1.48 (m, 2H), 1.20 (m, 2H).

EXAMPLE 327A

[1087] This example was made by substituting 2-(dimethylamino)ethyl chloride for 4-(2-chloroethyl)morpholine in EXAMPLE 322A.

EXAMPLE 327B

[1088] This example was made by substituting EXAMPLE 327A and phenylboronic acid for EXAMPLE 32B and 4-chlorophenylboronic acid, respectively, in EXAMPLE 32C.

EXAMPLE 327C

[1089] This example was made by substituting EXAMPLE 327B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 327D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(dimethylamino)ethoxy)piperidin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1090] This example was made by substituting EXAMPLE 327C and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 10.00 (m, 1H), 8.29 (s, 1H), 8.27 (d, 1H), 7.60 (dd, 1H), 7.49 (d, 2H), 7.10 (m, 10H), 6.93 (d, 1H), 6.77 (t, 2H), 6.68 (t, 1H), 6.60 (d, 2H), 3.63 (m, 2H), 3.29 (m, 6H), 2.85 (m, 6H), 1.51 (m, 1H), 1.33 (s, 6H), 1.25 (m, 2H), 1.08 (m, 1H), 1.0 (m, 2H).

EXAMPLE 328

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(dimethylamino)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1091] This example was made by substituting EXAMPLE 327C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.71 (s, 1H), 9.86 (m, 1H), 8.51 (t, 1H), 8.35 (s, 1H), 7.65 (dd, 1H), 7.44 (d, 2H), 7.15 (m, 14H), 6.58 (d, 2H), 3.43 (m, 2H), 3.13 (m, 2H), 3.13 (t, 2H), 3.03 (m, 6H), 2.76 (m, 6H), 1.51 (m, 1H), 1.24 (m, 2H), 0.97 (m, 2H).

EXAMPLE 329

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(dimethylamino)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[1092] This example was made by substituting EXAMPLE 327C and EXAMPLE 264B for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino).-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.72 (s, 1H), 9.75 (m, 1H), 8.23 (s, 1H), 8.17 (d, 1H), 7.58 (dd, 1H), 7.11 (m, 10H), 6.94 (d, 1H), 6.90 (d, 2H), 6.58 (d, 2H), 6.57 (d, 1H), 3.38 (m, 2H), 3.15 (m, 2H), 2.98 (m, 2H), 2.74 (m, 4H), 2.50 (s, 3H), 2.49 (s, 3H), 1.85 (m, 4H), 1.76 (m, 4H), 1.47 (m, 2H), 1.24 (m, 2H), 0.97 (m, 2H).

EXAMPLE 330A

[1093] This example was made by substituting 1-(2-chloroethyl)piperidine for 4-(2-chloroethyl)morpholine in EXAMPLE 322A.

EXAMPLE 330B

[1094] This example was made by substituting EXAMPLE 330A and phenylboronic acid for EXAMPLE 32B and 4-chlorophenylboronic acid, respectively, in EXAMPLE 32C.

EXAMPLE 330C

[1095] This example was made by substituting EXAMPLE 330B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 330D

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(piperidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1096] This example was made by substituting EXAMPLE 330C and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.97 (s, 1H), 10.27 (m, 1H), 8.51 (s, 1H), 8.49 (d, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.33 (m, 10H), 7.16 (d, 1H), 6.99 (t, 2H), 6.91 (t, 1H), 6.82 (d, 2H), 3.37 (m, 2H), 3.17 (m, 2H), 3.03 (s, 2H), 2.95 (m, 8H), 1.73 (m, 6H), 1.55 (s, 6H), 1.50 (m, 2H), 1.30 (m, 2H), 1.19 (m, 2H).

EXAMPLE 331

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(piperidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1097] This example was made by substituting EXAMPLE 330C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.95 (s, 1H), 10.16 (m, 1H), 8.74 (t, 1H), 8.58 (s, 1H), 7.89 (dd, 1H), 7.67 (d, 2H), 7.29 (m, 14H), 6.81 (d, 2H), 3.66 (m, 2H), 3.37 (m, 2H), 3.27 (t, 2H), 3.17 (m, 2H), 2.95 (m, 8H), 1.73 (m, 4H), 1.63 (m, 2H), 1.49 (m, 2H), 1.30 (m, 2H), 1.19 (m, 2H).

EXAMPLE 332

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-(2-(piperidin-1-yl)ethoxy)piperidin-1-yl)benzoyl)-3-nitro-4-((1-((phenylsulfanyl)methyl)cyclopentyl)amino)benzene-sulfonamide

[1098] This example was made by substituting EXAMPLE 330C and EXAMPLE 264B for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 11.97 (s, 1H), 10.27 (m, 1H), 8.47 (s, 1H), 8.40 (d, 1H), 7.82 (dd, 1H), 7.74 (d, 2H), 7.27 (m, 13H), 6.80 (m, 3H), 3.67 (m, 2H), 3.37 (m, 2H), 3.17 (m, 2H), 3.03 (s, 2H), 2.92 (m, 6H), 2.09 (m, 2H), 1.98 (m, 2H), 1.70 (m, 10H), 1.49 (m, 2H), 1.30 (m, 2H), 1.19 (m, 2H).

EXAMPLE 333A

[1099] This example was prepared by substituting (S)-3-(benzyloxycarbonyl)aminobutyrolactone, prepared as described in J. Am. Chem. Soc. 1986, 108, 4943-4952, for (R)-3-(benzyloxycarbonyl)aminobutyrolactone in EXAMPLE 19A.

EXAMPLE 333B

[1100] This example was prepared by substituting EXAMPLE 333A for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 333C

[1101] This example was prepared by substituting EXAMPLE 333B for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 333D

[1102] This example was prepared by substituting EXAMPLE 333C for EXAMPLE 19C in EXAMPLE 19D.

EXAMPLE 333E

[1103] This example was prepared by substituting EXAMPLE 333D for EXAMPLE 18C in EXAMPLE 18E.

EXAMPLE 333F

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1104] This example was made by substituting EXAMPLE 1C and EXAMPLE 333E for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.86 (s, 1H), 11.20 (m, 1H), 11.07 (m, 1H), 9.97 (m, 1H), 8.30 (d, 1H), 8.05 (2, 1H), 7.87 (dd, 1H), 7.60 (t, 1H), 7.53 (d, 2H), 7.06 (m, 13H), 6.69 (d, 2H), 4.12 (s, 2H), 3.62 (m, 4H), 3.11 (m, 5H), 2.95 (m, 4H), 2.78 (m, 8H), 1.51 (m, 2H).

EXAMPLE 334A

[1105] This example was made by substituting 4-hydoxyphenylboronic acid for 4-chlorophenylboronic acid in EXAMPLE 2B.

EXAMPLE 334B

[1106] A mixture of EXAMPLE 334A (0.24 g), 2-(dimethylamino)ethyl chloride (0.22 g), and K_2CO_3 (0.5 g) in acetone (20 mL) at reflux was stirred for 18 hours, concentrated, and treated with ethyl acetate and water. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5% 7M NH_3 in methanol/dichloromethane.

EXAMPLE 334C

[1107] This example was made by substituting EXAMPLE 334B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 334D

N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1108] This example was made by substituting EXAMPLE 334C for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.55 (m, 1H), 10.88 (m, 1H), 10.70 (m, 1H), 8.54 (d, 1H), 8.29 (d, 1H), 8.11 (dd, 1H), 7.78 (d, 2H), 7.49 (t, 2H), 7.20 (m, 10H), 6.93 (d, 2H), 4.42 (t, 2H), 4.36 (s, 2H), 4.29 (m, 1H), 3.86 (m, 2H), 3.52 (m, 2H), 3.39 (m, 2H), 3.13 (m, 6H), 2.82 (s, 3H), 2.83 (s, 3H), 2.70 (m, 8H), 2.20 (m, 2H).

EXAMPLE 335

N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1109] This example was made by substituting EXAMPLE 334C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.37 (m, 1H), 11.19 (m, 1H), 10.71 (m, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 8.06 (dd, 1H), 7.85 (dd, 2H), 7.78 (d, 2H), 7.50 (t, 2H), 7.20 (m, 10H), 6.93 (d, 2H), 4.41 (t, 2H), 4.36 (s, 2H), 4.28 (m, 1H), 3.92 (m, 2H), 3.80 (t, 2H), 3.52 (m, 2H), 3.39 (m, 2H), 3.23 (m, 8H), 2.98 (m, 2H), 2.84 (s, 6H), 2.25 (m, 2H).

EXAMPLE 336

N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1110] This example was made by substituting EXAMPLE 334C and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (s, 1H), 11.47 (m, 1H), 10.83 (m, 1H), 10.23 (m, 1H), 8.53 (s, 1H), 8.51 (d, 1H), 8.10 (m, 1H), 7.83 (dd, 1H), 7.80 (d, 2H), 7.50 (t, 2H), 7.39 (d, 1H), 7.31 (m, 3H), 7.25 (d, 2H), 7.10 (d, 2H), 7.01 (t, 2H), 6.93 (m, 3H), 4.41 (t, 2H), 4.36 (s, 2H), 3.86 (m, 2H), 3.38 (m, 2H), 3.20 (s, 2H), 3.23 (m, 2H), 2.98 (m, 2H), 3.01 (m, 4H), 2.84 (d, 3H), 2.73 (d, 3H), 1.56 (s, 6H).

EXAMPLE 337

N-(4-(4-((4'-(2-(dimethylamino)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1111] This example was made by substituting EXAMPLE 334C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (s, 1H), 11.39 (m, 1H), 10.73 (m, 1H), 10.13 (m, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 8.07 (m, 1H), 7.91 (dd, 1H), 7.76 (d, 2H), 7.50 (t, 2H), 7.25 (m, 10H), 7.09 (d, 2H), 6.92 (d, 2H), 4.41 (t, 2H), 4.36 (s, 2H), 3.86 (m, 2H), 3.67 (m, 2H), 3.28 (m, 2H), 3.20 (s, 2H), 3.01 (m, 4H), 2.84 (d, 3H), 2.73 (d, 3H).

EXAMPLE 338A

[1112] This example was made by substituting 4-(2-chloroethyl)morpholine for 2-(dimethylamino)ethyl chloride in EXAMPLE 334B.

EXAMPLE 338B

[1113] This example was made by substituting EXAMPLE 338A for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 338C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1114] This example was made by substituting EXAMPLE 338B for EXAMPLE 2C in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.89 (s, 1H), 11.50 (m, 1H), 11.30 (m, 1H), 10.46 (m, 1H), 8.31 (d, 1H), 8.06 (d, 1H), 7.88 (m, 1H), 7.55 (d, 2H), 7.27 (t, 2H), 6.98 (m, 11H), 6.70 (d, 2H), 4.28 (t, 2H), 4.13 (s, 2H), 3.68 (m, 4H), 3.33 (m, 2H), 3.28 (m, 2H), 3.06 (m, 6H), 2.78 (m, 6H), 2.48 (m, 6H), 1.97 (m, 2H).

EXAMPLE 339

N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1115] This example was made by substituting EXAMPLE 338B and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.47 (m, 1H), 11.28 (m, 1H), 11.13 (m 1H), 10.01 (m, 1H), 8.30 (d, 1H), 8.05 (d, 1H), 7.87 (m, 1H), 7.61 (dd, 1H), 7.54 (d, 2H), 7.26 (t, 2H), 6.96 (m, 11H), 6.70 (d, 2H), 4.26 (t, 2H), 4.12 (s, 2H), 4.07 (m, 1H), 3.63 (m, 6H), 3.33 (m, 2H), 3.27 (m, 2H), 3.05 (m, 6H), 2.79 (m, 8H), 1.52 (m, 2H).

EXAMPLE 340

4-((1,1-dimethyl-2-(phenylsulfanyl)ethyl)amino)-N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1116] This example was made by substituting EXAMPLE 338B and 4-(1,1-dimethyl-2-phenylsulfanylethylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.12 (s, 1H), 11.83 (m, 1H), 11.62 (m, 1H), 10.43 (m, 1H), 8.53 (s, 1H), 8.51 (d, 1H), 8.12 (m, 1H), 7.83 (dd, 1H), 7.80 (d, 2H), 7.49 (t, 2H), 7.39 (d, 1H), 7.31 (m, 3H), 7.25 (d, 2H), 7.10 (d, 2H), 6.99 (t, 2H), 6.93 (m, 3H), 4.51 (t, 2H), 4.36 (s, 2H), 3.91 (m, 2H), 3.35 (m, 8H), 3.02 (m, 8H), 1.56 (s, 6H).

EXAMPLE 341

N-(4-(4-((4'-(2-(morpholin-4-yl)ethoxy)(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1117] This example was made by substituting EXAMPLE 338B and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (s, 1H), 11.67 (m, 1H), 11.46 (m, 1H), 10.24 (m, 1H), 8.76 (t, 1H), 8.60 (d, 1H), 8.10 (m, 1H), 7.91 (dd, 1H), 7.76 (d, 2H), 7.50 (t, 2H), 7.26 (m, 10H), 7.10 (d, 2H), 6.92 (d, 2H), 4.50 (t, 2H), 4.36 (s, 2H), 3.91 (m, 4H), 3.35 (m, 10H), 3.01 (m, 8H).

EXAMPLE 342A

[1118] A mixture of EXAMPLE 30B (1.2 g) and pyridine (3 mL) in dichloromethane (10 mL) at 25°C was treated with p-toluenesulfonyl chloride (0.572 g), stirred for 18 hours, treated with dichloromethane (150 mL), washed with 5% HCl, water, and brine, and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 342B

[1119] A mixture of EXAMPLE 342A (1.7 g) and imidazole (0.42 g) in DMF (25 mL) at 60°C was stirred for 4 hours, treated with ethyl acetate (200 mL), washed with aqueous NH_4Cl, water, and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexane and 5% methanol/dichloromethane.

EXAMPLE 342C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1120] This example was made by substituting EXAMPLE 342B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.47 (d, 1H), 8.17 (d, 1H), 7.73 (m, 3H), 7.65 (s, 1H), 7.51 (dd, 1H), 7.37 (m, 2H), 7.19 (m, 10H), 6.93 (s, 1H), 6.82 (d, 2H), 6.63 (d, 1H), 4.09 (t, 2H), 3.87 (m, 1H), 3.31 (m, 8H), 3.15 (m, 4H), 2.23 (m, 2H).

EXAMPLE 343

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1121] This example was made by substituting EXAMPLE 342B for 4-(((1R)-3-(dimethylamino)-l-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (m, 1H), 9.06 (m, 1H), 8.53 (d, 1H), 8.23 (m, 2H), 8.08 (m, 1H), 7.82 (dd, 1H), 7.78 (d, 2H), 7.71 (t, 1H), 7.70 (d, 2H), 7.64 (t, 2H), 7.43 (m, 8H), 7.06 (m, 4H), 4.35 (s, 2H), 4.31 (t, 2H), 4.08 (m, 1H), 3.83 (m, 2H), 3.28 (m, 6H), 2.76 (m, 2H), 2.39 (m, 2H).

EXAMPLE 344

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxy-piperidin-1-yl)benzoyl)-4-(((1R)-3-(1H-imidazol-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1122] This example was made by substituting EXAMPLE 90C and EXAMPLE 342B for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.11 (m, 1H), 9.06 (m, 2H), 8.53 (d, 2H), 8.22 (m, 2H), 7.82 (dd, 1H), 7.71 (m, 4H), 7.64 (t, 1H), 7.26 (m, 10H), 6.99 (t, 2H), 6.83 (d, 1H), 4.31 (t, 2H), 4.04 (m, 1H), 3.37 (m, 5H), 3.19 (s, 3H), 2.89 (m, 3H), 2.39 (m, 2H), 1.46 (m, 2H), 1.17 (m, 2H).

EXAMPLE 345

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[1123] This example was made by substituting (R)-4-(4-(4-methylpiperazin-1-yl)-1-phenylsulfanylmethyl-butylamino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.12 (m, 1H), 10.89 (m, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 8.05 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 3H), 7.24 (m, 10H), 6.93 (d, 2H), 4.35 (s, 2H), 4.16 (m, 1H), 3.90 (m, 2H), 3.29 (m, 8H), 2.80 (m, 8H).

EXAMPLE 346

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzenesulfonamide

[1124] This example was made by substituting 4-(((1R)-2-((2-(dimethylamino)ethyl)(methyl)amino)-1-((phenylsulfanyl)methyl) ethyl)amino)-3-nitrobenzenesulfonamide(prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (m, 1H), 11.09 (m, 1H), 8.49 (d, 1H), 8.34 (d, 1H), 8.08 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 3H), 7.24 (m, 10H), 6.93 (d, 2H), 4.34 (s, 2H), 3.87 (m, 2H), 3.29 (m, 8H), 2.78 (m, 9H), 2.83 (m, 6H).

EXAMPLE 347

(4R)-4-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-5-(phenylsulfanyl)pentanamide

[1125] This example was made by substituting (4R)-4-((4-(aminosulfonyl)-2-nitrophenyl)amino)-N,N-dimethyl-5-(phenylsulfanyl)pentanamide, prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.53 (d, 1H), 8.31 (d, 1H), 7.83 (dd, 1H), 7.73 (d, 2H), 7.51 (m, 2H), 7.24 (m, 12H), 6.90 (d, 2H), 4.12 (m, 1H), 3.40 (m, 8H), 3.26 (m, 4H), 2.83 (s, 3H), 2.74 (s, 3H), 2.39 (m, 4H), 1.97 (m, 2H).

EXAMPLE 348A

[1126] A mixture of tert-butyl (2E,4R)-4-((tert-butoxycarbonyl)amino)-5-(phenylsulfanyl)pent-2-enoate, prepared as described in WO02/24636, (14 g) and tris(triphenylphosphine rhodium chloride (Wilkinson's catalyst) (2 g) in toluene (250 mL) at 45°C was stirred under hydrogen (balloon) for 48 hours, filtered through silica gel and concentrated.

EXAMPLE 348B

[1127] EXAMPLE 348A (6.3 g) in dichloromethane at 25°C was treated with meta-chloroperbenzoic acid (8.8 g), stirred for 6 hours, poured into ethyl acetate, washed with aqueous sodium carbonate and brine, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 348C

[1128] This example was made by substituting EXAMPLE 348B for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 348D

[1129] EXAMPLE 348C (5.1 g), dimethylamine hydrochloride (2.33 g), EDAC·HCl (8.21 g), DMAP (1.74 g), and TEA (3.97 mL) in dichloromethane (75 mL) at 25°C was stirred for 24 hours, poured into water, and extracted with ethyl acetate. The extract was washed with water and brine and concentrated. The concentrate was flash chromatogrphed on silica gel with 10% methanol/ethyl acetate.

EXAMPLE 348E

[1130] This example was made by substituting EXAMPLE 348D for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 348F

[1131] This example was made by substituting EXAMPLE 348E for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 348G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-(dimethylamino)-1-((phenylsulfonyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[1132] This example was made by substituting for EXAMPLE 348F for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.14 (m, 1H), 10.90 (m, 1H), 9.82 (m, 1H), 8.50 (d, 1H), 8.12 (d, 1H), 8.05 (m, 1H), 7.90 (dd, 1H), 7.80 (d, 2H), 7.45 (m, 12H), 6.93 (d, 2H), 4.35 (s, 2H), 4.22 (m, 1H), 3.89 (m, 2H), 3.28 (m, 4H), 2.96 (m, 4H), 2.80 (m, 4H), 2.68 (m, 6H), 1.71 (m, 4H).

EXAMPLE 349

2-(((3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butyl)(methyl)amino)-N,N-dimethylacetamide

[1133] A mixture of EXAMPLE 26H (45 mg), 2-chloro-N,N-dimethylacetamide (50 mg), and DIEA (0.2 mL) in dioxane(1 mL) at 80°C was stirred for 18 hours and concentrated. The concentrate was flash chromatographed on silca gel with 5% 7M NH_3 in methanol/dichloromethane. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.13 (m, 1H), 11.31 (m, 1H), 9.58 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.11 (m, 1H), 7.87 (m, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 10H), 6.93 (d, 2H), 4.35 (s, 2H), 4.23 (m, 1H), 4.21 (s, 2H), 3.89 (m, 2H), 3.27 (m, 8H), 2.88 (m, 6H), 2.78 (s, 3H), 2.22 (m, 2H).

EXAMPLE 350

(3R)-N-(tert-butyl)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanamide

[1134] This example was made by substituting tert-butylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.03 (m, 1H), 9.58 (m, 1H), 8.70 (d, 1H), 8.52 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.67 (s, 1H), 7.53 (m, 4H), 7.25 (m, 10H), 6.93 (d, 2H), 4.37 (m, 2H), 3.89 (m, 2H), 2.98 (m, 8H), 2.62 (dd, 2H), 1.15 (s, 9H).

EXAMPLE 351

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-diisopropyl-4-(phenylsulfanyl)butanamide

[1135] This example was made by substituting diisopropylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (m, 1H), 9.61 (m, 1H), 8.79 (d, 1H), 8.52 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.54 (m, 3H), 7.25 (m, 10H), 6.93 (d, 2H), 4.41 (m, 2H), 3.96 (m, 3H), 2.98 (m, 8H), 2.84 (m, 2H), 1.14 (m, 12H).

EXAMPLE 352

(3R)-N-(tert-butyl)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-methyl-4-(phenylsulfanyl)butanamide

[1136] This example was made by substituting N-methyl-tert-butylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (m, 1H), 9.59 (m, 1H), 8.80 (d, 1H), 8.53 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.52 (m, 3H), 7.25 (m, 10H), 6.93 (d, 2H), 4.42 (m, 2H), 3.92 (m, 1H), 2.98 (m, 8H), 2.80 (s, 3H), 2.84 (m, 2H), 1.27 (s, 9H).

EXAMPLE 353

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-N-methyl-4-(phenylsulfanyl)butanamide

[1137] This example was made by substituting N-methyl-isopropylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.07 (m, 1H), 9.62 (m, 1H), 8.82 (d, 1H), 8.53 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.25 (m, 10H), 6.93 (d, 2H), 4.61 (m, 1H), 4.43 (m, 2H), 4.05 (m, 1H), 3.92 (m, 1H), 2.98 (m, 8H), 2.72 (s, 3H), 2.84 (m, 2H), 0.99 (m, 6H).

EXAMPLE 354

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-3-oxo-1-((phenylsulfanyl)methyl)-3-(piperidin-1-yl)propyl)amino)benzenesulfonamide

[1138] This example was made by substituting piperidine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.06 (m, 1H), 9.62 (m, 1H), 8.79 (d, 1H), 8.53 (d, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.52 (m, 3H), 7.25 (m, 10H), 6.93 (d, 2H), 4.44 (m, 2H), 3.89 (m, 1H), 3.35 (m, 4H), 2.99 (m, 8H), 3.00 (dd, 2H), 2.75 (dd, 2H), 1.42 (m, 6H).

EXAMPLE 355A

[1139] This example was made by substituting tert-butyl (5R)-5-((4-(aminosulfonyl)-2-nitrophenyl)amino)-6-(phenylsulfanyl)hexylcarbamate(prepared as described in WO 02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 355B

[1140] A mixture of EXAMPLE 355A (100 mg) and TFA (1 mL) in dichloromethane (1 mL) at 25°C were stirred for 2 hours and concentrated. The concentrate was flash chromatographed on silica gel with 5-10% (7M NH_3 in methanol)/dichloromethane.

EXAMPLE 355C

N-((5R)-5-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-6-(phenylsulfanyl)hexyl)-2-(dimethylamino)acetamide

[1141] A mixture of EXAMPLE 355B (50 mg), N,N-dimethylglycine (23 mg), EDAC·HCl (42 mg) and DMAP (27.2 mg) in dichloromethane (2 mL) at 25°C was stirred for 18 hours, treated with ethyl acetate, washed with aqueous $NaHCO_3$, water and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 5-10% 7M NH_3 in methanol/dichloromethane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 11.53 (m, 1H), 9.92 (m, 1H), 8.63 (t, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 8.16 (m, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.52 (m, 3H), 7.22 (m, 8H), 6.93 (d, 2H), 4.33 (s, 2H), 4.10 (m, 1H), 3.85 (m, 2H), 3.37 (m, 4H), 3.12 (m, 8H), 2.84 (m, 6H), 1.76 (m, 2H), 1.34 (m, 4H).

EXAMPLE 356

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N,N-dimethyl-4-(phenylsulfanyl)butanamide

[1142] This example was made by substituting dimethylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.83 (d, 1H), 8.52 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.45 (m, 7H), 7.18 (m 6H), 6.90 (d, 2H), 4.40 (m, 1H), 3.40 (m, 4H), 3.25 (m, 4H), 2.96 (dd, 2H), 2.89 (s, 3H), 2.78 (s, 3H), 2.70 (dd, 2H), 2.45 (m 2H).

EXAMPLE 357

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1,1-dioxidothiomorpholin-4-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1143] This example was made by substituting thiomorpholine 1,1-dioxide, prepared as described in J. Med. Chem 1994, 37, 913-933, for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (d, 1H), 8.47 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 13H), 6.83 (d, 2H), 3.82 (m, 4H), 3.39 (m, 4H), 3.18 (m, 8H), 3.04 (m, 3H), 2.89 (dd, 2H), 2.40 (m, 2H).

EXAMPLE 358

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanamide

[1144] This example was made by substituting 0.5M NH_3 in dioxane for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.57 (d, 1H), 8.46 (d, 1H), 7.79 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 13H), 6.83 (d, 2H), 4.33 (m, 2H), 3.39 (m, 2H), 3.33 (m, 2H), 3.18 (m, 5H), 2.60 (m, 4H), 2.40 (m, 2H).

EXAMPLE 359

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-cyclopropyl-4-(phenylsulfanyl)butanamide

[1145] This example was made by substituting cyclopropylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.60 (d, 1H), 8.48 (d, 1H), 8.11 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 12H), 6.83 (d, 2H), 4.32 (m, 2H), 3.39 (m, 2H), 3.34 (m, 2H), 3.20 (m, 5H), 2.56 (m, 4H), 2.40 (m 2H), 0.54 (m, 2H), 0.29 (m, 2H).

EXAMPLE 360

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-cyclobutyl-4-(phenylsulfanyl)butanamide

[1146] This example was made by substituting cyclobutylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.63 (d, 1H), 8.48 (d, 1H), 8.27 (d, 1H), 7.80 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 12H), 6.85 (d, 2H), 4.33 (m, 2H), 4.10 (m, 1H), 3.40 (m, 2H), 3.38 (m, 2H), 3.20 (m, 5H), 2.57 (m, 4H), 2.40 (m 2H), 2.08 (m, 2H), 1.77 (m, 2H), 1.58 (m, 2H).

EXAMPLE 361

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-l-yl)benzoyl)-4-(((1R)-3-(4-methylpiperazin-1-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1147] This example was made by substituting 1-methylpiperazine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (m, 1H), 10.52 (m, 1H), 8.73 (m, 1H), 8.53 (d, 1H), 7.84 (dd, 1H), 7.76 (d, 2H), 7,53 (m 4H), 7.24 (m, 10H), 6.93 (d, 2H), 4.37 (m, 3H), 3.96 (m, 4H), 3.28 (m, 6H), 3.20 (m, 5H), 2.88 (m, 4H), 2.75 (m 3H), 2.54 (m, 2H).

EXAMPLE 362

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1148] This example was made by substituting morpholine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.69 (d, 1H), 8.50 (d, 1H), 7.81 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 12H), 6.86 (d, 2H), 4.39 (m, 2H), 3.44 (m, 13H), 3.32 (m, 2H), 2.98 (dd, 2H), 2.77 (dd, 2H), 2.40 (m, 2H).

EXAMPLE 363

4-(((1R)-3-(azetidin-1-yl)-3-oxo-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1149] This example was made by substituting azetidine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.71 (d, 1H), 8.50 (d, 1H), 7.81 (dd, 1H), 7.73 (d, 2H), 7.31 (m, 12H), 6.86 (d, 2H), 4.31 (m, 1H), 4.04 (t, 2H), 3.79 (m, 2H), 3.40 (m, 4H), 3.23 (m, 4H), 2.64 (dd, 2H), 2.52 (dd, 2H), 2.40 (m, 2H), 2.12 (m, 2H).

EXAMPLE 364

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-(2-(morpholin-4-yl)ethyl)-4-(phenylsulfanyl)butanamide

[1150] This example was made by substituting 4-(2-aminoethyl)morpholine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.52 (m, 1H), 8.74 (d, 1H), 8.51 (d, 1H), 8.45 (t, 1H), 7.83 (dd, 1H), 7.77 (d, 2H), 7.54 (m, 3H), 7.24 (m, 10H), 6.92 (d, 2H), 4.40 (m, 1H), 4.35 (m, 2H), 3.89 (m, 4H), 3.72 (m, 4H), 3.39 (m, 6H), 3.20 (m, 4H), 3.10 (m, 2H), 2.88 (m, 2H), 2.73 (m, 2H).

EXAMPLE 365

(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroaniline)-N-methyl-4-(phenylsulfanyl)butanamide

[1151] This example was made by substituting methylamine for isopropylamine in EXAMPLE 28. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.59 (d, 1H), 8.45 (d, 1H), 7.98 (m, 1H), 7.78 (dd, 1H), 7.73 (d, 2H), 7.32 (m, 12H), 6.83 (d, 2H), 4.30 (m, 1H), 3.39 (s, 2H), 3.29 (m, 2H), 3.18 (m, 4H), 2.61 (m, 4H), 2.53 (d, 3H), 2.40 (m, 2H).

EXAMPLE 366

4-(((1R)-3-amino-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1152] This example was made by substituting 7M NH_3 in methanol for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.43 (d, 1H), 8.08 (d, 1H), 7.83 (dd, 1H), 7.72 (d, 2H), 7.31 (m, 12H), 6.93 (m, 1H), 6.78 (d, 2H), 4.10 (m, 2H), 3.38 (s, 2H), 3.33 (m, 2H), 3.12 (m, 5H), 2.87 (t, 2H), 2.40 (m, 2H), 2.00 (m, 2H).

EXAMPLE 367

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-cyano-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1153] This example was made by substituting sodium cyanide for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (d, 1H), 8.22 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.31 (m, 12H), 7.04 (d, 1H), 6.87 (d, 2H), 4.11 (m, 2H), 3.35 (m, 4H), 3.22 (m, 5H), 2.60 (t, 2H), 2.39 (m, 2H), 2.09 (m, 2H).

EXAMPLE 368

4-(((1R)-3-(tert-butylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1154] This example was made by substituting tert-butylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.94 (m, 1H), 8.75 (m, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 8.05 (m, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.23 (m, 10H), 6.93 (d, 2H), 4.34 (m, 2H), 3.88 (m, 2H), 3.42 (d, 2H), 3.27 (m, 5.H), 2.89 (m, 4H), 2.14 (m, 2H), 1.24 (s, 9H).

EXAMPLE 369

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1155] This example was made by substituting cyclopropylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.84 (m, 1H), 9.04 (m, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 8.02 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.35 (m, 3H), 3.88 (m, 2H), 3.27 (m, 5H), 3.09 (m, 2H), 2.87 (m, 2H), 2.66 (m, 2H), 2.14 (m, 2H), 0.82 (m, 2H), 0.70 (m, 2H).

EXAMPLE 370

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(cyclobutylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1156] This example was made by substituting cylcobutylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.88 (m, 1H), 9.04 (m, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 8.04 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.35 (m, 3H), 3.88 (m, 2H), 3.61 (m, 2H), 3.27 (m, 6H), 2.86 (m, 4H), 2.71 (m, 1H), 2.11 (m, 4H), 1.76 (m, 2H).

EXAMPLE 371

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1157] This example was made by substituting diethylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.99 (m, 1H), 10.08 (m, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 8.06 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.34 (m, 3H), 3.88 (m, 2H), 3.39 (m, 2H), 3.27 (m, 6H), 3.08 (m, 4H), 2.81 (m, 2H), 2.15 (m, 2H), 1.17 (m, 6H).

EXAMPLE 372

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1158] This example was made by substituting N-methylisopropylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.89 (m, 1H), 9.96 (m, 1H), 8.53 (d, 1H), 8.29 (m, 1H), 8.04 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.34 (m, 3H), 3.88 (m, 2H), 3.42 (m, 2H), 3.27 (m, 6H), 2.86 (m, 2H), 2.60 (m, 3H), 2.15 (m, 2H), 1.19 (m, 6H).

EXAMPLE 373

4-(((1R)-3-(tert-butyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1159] This example was made by substituting N-methyl-tert-butylamine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.84 (m, 1H), 9.70 (m, 1H), 8.53 (d, 1H), 8.30 (t, 1H), 8.03 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.52 (m, 4H), 7.23 (m, 8H), 6.93 (d, 2H), 4.35 (m, 3H), 3.88 (m, 2H), 3.43 (m, 2H), 3.27 (m, 6H), 2.86

(m, 2H), 2.64 (m, 3H), 2.22 (m, 2H), 1.29 (d, 9H).

EXAMPLE 374

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(piperidin-1-yl)propyl)amino)benzenesulfonamide

[1160] This example was made by substituting piperidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.95 (m, 1H), 9.97 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.04 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 4H), 7.23 (m, 8H), 6.93 (d, 2H), 4.35 (m, 2H), 4.22 (m, 1H), 3.88 (m, 2H), 3.40 (m, 2H), 3.27 (m, 6H), 3.10 (m, 2H), 2.81 (m, 6H), 2.22 (m, 2H), 1.75 (m, 4H), 1.35 (m, 2H).

EXAMPLE 375

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-hydroxypiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1161] This example was made by substituting 4-hydroxypiperidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.85 (m, 1H), 9.98 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.04 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.22 (m, 1H), 3.93 (m, 3H), 3.27 (m, 6H), 3.10 (m, 2H), 2.87 (m, 4H), 2.22 (m, 2H), 1.91 (m, 4H), 1.70 (m, 2H).

EXAMPLE 376

4-(((1R)-3-(4-acetylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(9-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1162] This example was made by substituting 1-acetylpiperazine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.69 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 7.99 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 4H), 7.23 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.22 (m, 1H), 3.92 (m, 2H), 3.41 (m, 4H), 3.27 (m, 6H), 3.00 (m, 2H), 2.85 (m, 6H), 2.22 (m, 2H), 2.02 (s, 3H).

EXAMPLE 377

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(thiomorpholin-4-yl)propyl)amino)benzenesulfonamide

[1163] This example was made by substituting thiomorpholine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.69 (m, 1H), 10.55 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 7.99 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.25 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.25 (m, 1H), 3.90 (m, 2H), 3.64 (m, 4H), 3.41 (m, 4H), 3.17 (m, 9H), 2.82 (m, 4H), 2.22 (m, 2H).

EXAMPLE 378

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2-(morpholin-4-yl)ethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1164] This example was made by substituting 4-(2-aminoethyl)morpholine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.63 (m, 1H), 9.26 (m, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 7.99 (m, 1H), 7.86 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.25 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.25 (m, 1H), 3.90 (m, 2H), 3.77 (m, 2H), 3.41 (m, 4H), 3.27 (m, 6H), 3.05 (m, 6H), 2.82 (m, 4H), 2.17 (m, 2H).

EXAMPLE 379A

[1165] This.example was made by substituting tert-butyl 1-piperazinecaboxylate for isopropylamine in example 35B.

EXAMPLE 379B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(piperazin-1-yl)propyl)amino)benzenesulfonamide

[1166] This example was made by substituting EXAMPLE 379A for EXAMPLE 27B in EXAMPLE 29A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.90 (m, 1H), 9.50 (m, 1H), 8.53 (d, 1H), 8.30 (d, 1H), 8.04 (m, 1H), 7.84 (dd, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.22 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.27 (m, 1H), 3.90 (m, 2H), 3.40 (m, 6H), 3.17 (m, 10H), 2.86 (m, 2H), 2.23 (m, 2H).

EXAMPLE 380

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((3R)-3-hydroxypyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1167] This example was made by substituting (S)-3-hydroxypyrrolidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.73 (m, 1H), 10.26 (m, 1H), 8.53 (d, 1H), 8.29 (d, 1H), 8.04 (m, 1H), 7.85 (m, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.35 (m, 3H), 3.88 (m, 2H), 3.38 (m, 4H), 3.17 (m, 6H), 3.03 (m, 1H), 2.87 (m, 4H), 2.17 (m, 2H), 1.91 (m, 2H).

EXAMPLE 381A

[1168] This example was made by substituting 3(R)-(tert-butoxycarbonylamino)pyrrolidine for isopropylamine in example 35B.

EXAMPLE 381B

4-(((1R)-3-((3R)-3-aminopyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1169] This example was made by substituting EXAMPLE 381A for EXAMPLE 27B in EXAMPLE 29A. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 11.09 (m, 1H), 10.92 (m, 1H), 8.53 (d, 1H), 8.47 (m, 1H), 8.30 (d, 1H), 8.04 (m, 1H), 7.85 (m, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.23 (m, 8H), 6.93 (d, 2H), 4.35 (m, 3H), 3.88 (m, 2H), 3.40 (m, 4H), 3.27 (m, 6H), 3.08 (m, 1H), 2.86 (m, 4H), 2.22 (m, 2H), 2.05 (m, 2H).

EXAMPLE 382

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(3-hydroxyazetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1170] This example was made by substituting 3-hydroxyazetidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.73 (m, 1H), 10.23 (m, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 8.00 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.52 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.35 (m, 2H), 4.26 (m, 3H), 4.04 (m, 1H), 3.88 (m, 2H), 3.71 (m, 2H), 3.24 (m, 8H), 2.86 (m, 2H), 1.98 (m, 2H).

EXAMPLE 383

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-methylpiperazin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1171] This example was made by substituting 1-methylpiperazine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.91 (m, 1H), 8.53 (d, 1H), 8.31 (d, 1H), 8.04 (m, 1H), 7.85 (dd, 1H), 7.78 (d, 2H), 7.54 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.34 (m, 2H), 4.26 (m, 1H), 3.88 (m, 2H), 3.40 (m, 6H), 3.27 (m, 8H), 2.86 (m, 4H), 2.80 (s, 3H), 2.21 (m, 2H).

EXAMPLE 384

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(1,1-dioxidothiomorpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1172] This example was made by substituting thiomorpholine 1,1-dioxide, prepared as described in J. Med. Chem 1994, 37, 913-933, for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.08 (m, 1H), 10.97 (m, 1H), 8.53 (d, 1H), 8.31 (d, 1H), 8.04 (m, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.53 (m, 4H), 7.23 (m, 8H), 6.93 (d, 2H), 4.35 (m, 2H), 4.26 (m, 2H), 3.88 (m, 2H), 3.55 (m, 5H), 3.24 (m, 8H), 2.89 (m, 4H), 1.98 (m, 2H).

EXAMPLE 385

4-(((1R)-3-(1,3-benzodioxol-5-ylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1173] This example was made by substituting 3,4-methylenedioxyaniline for isopropylamine in example 35B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (m, 1H), 11.29 (m, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.12 (m, 1H), 7.82 (dd, 1H), 7.77 (d, 2H), 7.53 (m, 4H), 7.24 (m, 9H), 6.93 (m, 4H), 6.07 (s, 2H), 4.35 (m, 2H), 4.26 (m, 2H), 3.28 (m, 9H), 2.85 (m, 4H), 2.15 (m, 2H).

EXAMPLE 386

4-(((1R)-3-((1,3-benzodioxol-4-ylmethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1174] This example was made by substituting 3,4-methylenedioxybenzylamine for isopropylamine in example 35B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (m, 1H), 11.29 (m, 1H), 9.26 (m, 1H), 8.53 (d, 1H), 8.26 (d, 1H), 8.11 (m, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.53 (m, 4H), 7.24 (m, 9H), 6.90 (m, 4H), 6.02 (s, 2H), 4.34 (m, 3H), 3.98 (m, 2H), 3.87 (m, 2H), 3.61 (m, 2H), 3.28 (m, 4H), 2.91 (m, 4H), 2.16 (m, 2H).

EXAMPLE 387

N-(4-(4-((4'-chloro(1,1'-biphenyl)- 2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-2-ylmethyl)amino)propyl)amino)benzenesulfonamide

[1175] This example was made by substituting 2-aminomethylpyridine for isopropylamine in example 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.11 (m, 1H), 11.57 (m, 1H), 9.46 (m, 3H), 8.53 (d, 1H), 8.26 (d, 1H), 8.11 (m, 1H), 7.86 (m, 1H), 7.78 (d, 2H), 7.51 (m, 4H), 7.24 (m, 9H), 6.93 (d, 2H), 4.33 (m, 2H), 4.26 (m, 1H), 3.87 (m, 2H), 3.39 (m, 4H), 3.25 (m, 4H), 2.84 (m, 4H), 2.22 (m, 2H).

EXAMPLE 388

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((2-(pyridin-2-yl)ethyl)amino)propyl)amino)benzenesulfonamide

[1176] This example was made by substituting 2-aminoethylpyridine for isopropylamine in example 35B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (m, 1H), 11.36 (m, 1H), 9.29 (m, 3H), 8.62 (d, 1H), 8.53 (d, 1H), 8.28 (d, 1H), 8.13 (m, 1H), 7.86 (d, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.18 (m, 9H), 6.93 (d, 2H), 4.33 (m, 2H), 3.87 (m, 2H), 3.31 (m, 7H), 3.05 (m, 4H), 2.84 (m, 4H), 2.18 (m, 2H).

EXAMPLE 389

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-((pyridin-4-ylmethyl)amino)propyl)amino)benzenesulfonamide

[1177] This example was made by substituting 4-aminomethylpyridine for isopropylamine in example 35B. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (m, 1H), 11.30 (m, 1H), 9.85 (m, 2H), 9.17 (m, 1H), 8.76 (d, 1H), 8.53 (d, 1H), 8.27 (d, 1H), 8.11 (m, 1H), 7.85 (d, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.19 (m, 9H), 6.93 (d, 2H), 4.33 (m, 2H), 4.23 (m, 1H), 3.87

(m, 2H), 3.29 (m, 6H), 3.05 (m, 2H), 2.84 (m, 4H), 2.23 (m, 2H).

EXAMPLE 390

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-ylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1178] This example was made by substituting 4-aminomorpholine for isopropylamine in example 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (m, 1H), 11.55 (m, 1H), 9.39 (m, 3H), 8.54 (d, 1H), 8.32 (d, 1H), 8.11 (m, 1H), 7.87 (d, 1H), 7.77 (d, 2H), 7.51 (m, 4H), 7.24 (m, 8H), 6.92 (d, 2H), 4.33 (m, 2H), 4.23 (m, 1H), 4.00 (m, 1H), 3.87 (m, 2H), 3.31 (m, 9H), 3.05 (m, 4H), 2.84 (m, 4H), 2.33 (m, 2H).

EXAMPLE 391

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methyl(pyridin-4-yl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1179] This example was made by substituting N-methyl-4-aminopyridine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.83 (m, 1H), 8.68 (m, 3H), 8.52 (d, 1H), 8.19 (t, 2H), 8.01 (m, 1H), 7.83 (d, 1H), 7.77 (d, 2H), 7.52 (m, 4H), 7.25 (m, 8H), 7.01 (d, 1H), 6.93 (d, 2H), 6.74 (m, 2H), 4.33 (m, 2H), 4.24 (m, 2H), 3.87 (m, 3H), 3.36 (m 4H), 3.26 (m, 4H), 2.83 (d, 3H), 2.33 (m, 2H).

EXAMPLE 392

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyridin-3-ylamino)propyl)amino)benzenesulfonamide

[1180] This example was made by substituting 3-aminopyridine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.80 (m, 1H), 8.72 (m, 3H), 8.52 (d, 1H), 8.22 (d, 2H), 7.99 (m, 1H), 7.83 (d, 1H), 7.77 (d, 2H), 7.52 (m, 4H), 7.19 (m, 8H), 7.02 (d, 1H), 6.93 (d, 2H), 6.59 (m, 1H), 4.52 (m, 2H), 4.33 (m, 2H), 4.12 (m, 1H), 3.87 (m, 2H), 3.36 (m 4H), 3.26 (m, 2H), 2.85 (d, 2H), 2.40 (m, 2H).

EXAMPLE 393

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1181] This example was made by substituting 2,6-dimethylpiperidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (m, 1H), 10.62 (m, 1H), 9.74 (m, 1H), 8.64 (m, 1H), 8.50 (d, 1H), 8.30 (d, 1H), 7.99 (m, 1H), 7.86 (d, 1H), 7.77 (d, 2H), 7.5 2 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 3.88 (m, 2H), 3.31 (m 9H), 2.85 (d, 4H), 2.15 (m, 2H), 1.79 (m, 2H), 1.64 (m, 4H), 1.26 (m, 6H).

EXAMPLE 394

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,6S)-2,6-dimethylpiperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1182] This example was made by substituting cis-2,6-dimethylpiperidine for isopropylamine in example 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.10 (m, 1H), 10.78 (m, 1H), 9.80 (m, 1H), 8.74 (m, 1H), 8.50 (d, 1H), 8.30 (d, 1H), 8.01 (m, 1H), 7.86 (d, 1H), 7.77 (d, 2H), 7.52 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.35 (m, 2H), 3.88 (m, 2H), 3.31 (m 9H), 2.85 (d, 4H), 2.15 (m, 2H), 1.79 (m, 2H), 1.64 (m, 4H), 1.26 (m, 6H).

EXAMPLE 395

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-ylamino)propyl)amino)benzenesulfonamide

[1183] This example was made by substituting 1-aminopyrrolidine for isopropylamine in example 35B. ^{1}H NMR (300

MHz, DMSO-d_6) δ 12.12 (m, 1H), 10.86 (m, 1H), 8.73 (m, 1H), 8.54 (d, 1H), 8.32 (d, 1H), 8.02 (m, 1H), 7.86 (d, 1H), 7.77 (d, 2H), 7.52 (m, 4H), 7.25 (m, 8H), 6.93 (d, 2H), 4.36 (m, 2H), 4.22 (m, 1H), 3.88 (m, 2H), 3.31 (m 10H), 2.85 (d, 4H), 2.32 (m, 2H), 2.11 (m, 4H).

EXAMPLE 396A

[1184] A mixture of tert-butyl 4-oxo-1-piperidinecarboxylate (2 g), methoxylamine hydrochloride (0.85 g), and potassium acetate (0.98 g) in ethanol(40 mL) was stirred at reflux for 18 hours and concentrated. The concentrate was treated with ethyl acetate (200 mL), washed with water and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was used without further purification.

EXAMPLE 396B

[1185] A mixture of EXAMPLE 396A (2.1 g) and TFA (10 mL) in dichloromethane (10 mL) at 25°C was stirred for 4 hours and concentrated.

EXAMPLE 396C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(4-(methoxyimino)piperidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1186] This example was made by substituting EXAMPLE 396B for isopropylamine in EXAMPLE 35B. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.51 (d, 1H), 7.82 (dd, 1H), 7.72 (d, 2H), 7.52 (m, 4H), 7.32 (m, 10H), 6.87 (d, 2H), 4.17 (m, 1H), 3.71 (s, 3H), 3.32 (m 10H), 2.73 (m, 2H), 2.40 (m, 6H), 2.25 (m, 4H), 1.91 (m, 2H).

EXAMPLE 397

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(2H-tetrazol-5-yl)propyl)amino)benzenesulfonamide

[1187] A mixture of EXAMPLE 367 (80 mg), sodium azide (33 mg), and ammonium chloride (27 mg) in DMF (2 mL) at 110°C was stirred for 18 hours, treated with ethyl acetate (100 mL), washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 3% methanol/dichloromethane. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.09 (m, 1H), 10.15 (m, 1H), 8.52 (d, 1H), 8.32 (d, 1H), 7.82 (dd, 1H), 7.78 (d, 2H), 7.52 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.37 (m, 2H), 4.20 (m, 1H), 3.71 (s, 3H), 3.28 (m, 5H), 2.98 (t, 2H), 2.83 (m, 2H), 2.23 (m, 2H).

EXAMPLE 398A

[1188] This example was made by substituting 4-bromo-3-trifluoromethylbenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 398B

[1189] A mixture of EXAMPLE 27B (2 g) and diethylamine (5 mL) in THF (20 mL) at 25°C was stirred for 18 hours and concentrated. The concentrate was flash chromatographed on silica gel with 3% (7M NH_3 in methanol)/dichloromethane.

EXAMPLE 398C

[1190] This example was made by substituting EXAMPLE 398A and EXAMPLE 398B for EXAMPLE 164B and 164A, respectively, in EXAMPLE 164C.

EXAMPLE 398D

[1191] This example was made by substituting EXAMPLE 398C for EXAMPLE 27D in EXAMPLE 27E.

EXAMPLE 398E

[1192] This example was made by substituting EXAMPLE 398D for EXAMPLE 27E in EXAMPLE 34.

EXAMPLE 398F

[1193] This example was made by substituting EXAMPLE 398E for EXAMPLE 34 in EXAMPLE 35A.

EXAMPLE 398G

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1194] This example was made by substituting EXAMPLE 398F and diisopropylamine for EXAMPLE 35A and isopropylamine, respectively, in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (m, 1H), 11.07 (m, 1H), 9.25 (m, 1H), 8.06 (m, 1H), 7.93 (d, 1H), 7.82 (dd, 1H), 7.74 (d, 2H), 7.51 (m, 4H), 7.27 (m, 8H), 6.93 (t, 2H), 6.08 (d, 1H), 4.33 (m, 2H), 4.00 (m, 1H), 3.87 (m, 2H), 3.55 (m, 4H), 3.28 (m, 4H), 2.90 (m, 4H), 2.17 (m, 2H), 1.22 (m, 12H).

EXAMPLE 399

N-(4-(4-((4'-chloro(l,l'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1195] This example was made by substituting EXAMPLE 398F for EXAMPLE 35A in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.95 (m, 1H), 11.11 (m, 1H), 8.74 (m, 1H), 8.06 (m, 1H), 7.94 (d, 1H), 7.91 (s, 1H), 7.81 (dd, 1H), 7.74 (d, 2H), 7.51 (m, 4H), 7.26 (m, 6H), 6.96 (d, 1H), 6.91 (d, 2H), 5.99 (d, 1H), 4.33 (m, 2H), 4.03 (m, 1H), 3.87 (m, 2H), 3.31 (m, 5H), 2.88 (m, 6H), 2.07 (m, 2H), 1.18 (m, 6H).

EXAMPLE 400

4-(((1R)-3-(bis(2-hydroxyethyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1196] This example was made by substituting diethanolamine for isopropylamine in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.58 (d, 1H), 8.30 (m, 1H), 8.01 (s, 1H), 7.93 (dd, 1H), 7.82 (d, 2H), 7.41 (m, 11H), 7.10 (d, 1H), 6.93 (d, 2H), 4.50 (m, 1H), 4.23 (m, 1H), 3.75 (m, 4H), 3.49 (m, 4H), 3.28 (m, 4H), 3.33 (m, 7H), 2.59 (m, 2H), 2.23 (m, 2H).

EXAMPLE 401A

[1197] A mixture of 1-bromo-2-(trifluoromethoxy)benzene (5 g) and chlorosulfonic acid (30 mL) at 85°C were stirred for 18 hours, treated with crushed ice, and extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate in IPA (200 mL) at 0°C was treated with 38% ammonium hydroxide (50 mL), stirred for 18 hours and concentrated. The concentrate was treated with ethyl acetate (200 mL) and water. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 401B

[1198] This example was made by substituting EXAMPLE 401A for EXAMPLE 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 401C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-4-(trifluoromethoxy)benzenesulfonamide

[1199] This example was made by substituting EXAMPLE 401B for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.92 (m, 1H), 11.12 (m, 1H), 10.18 (m, 1H), 7.92 (d, 1H), 7.56 (d, 2H), 7.31 (m, 4H), 7.08 (m, 6H), 6.73 (d, 2H), 5.86 (d, 1H), 4.15 (m, 2H), 3.68 (m, 2H), 3.59 (m, 1H), 3.09 (m, 4H), 2.91 (m, 4H), 2.66 (m, 2H), 2.31

(m, 6H), 1.95 (m, 2H).

EXAMPLE 402

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropyl(methyl)amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1200] This example was made by substituting EXAMPLE 398F and methylisopropylamine for EXAMPLE 35A and isopropylamine, respectively, in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (m, 1H), 11.40 (m, 1H), 10.39 (m, 1H), 8.14 (m, 1H), 7.95 (d, 1H), 7.81 (d, 1H), 7.76 (d, 2H), 7.53 (m, 4H), 7.28 (m, 7H), 6.93 (m, 3H), 6.03 (m, 1H), 4.33 (m, 2H), 4.02 (m, 1H), 3.87 (m, 2H), 3.32 (m, 6H), 3.04 (m, 2H), 2.86 (m, 2H), 2.57 (m, 3H), 2.19 (m, 2H), 1.19 (m, 6H).

EXAMPLE 403

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1201] This example was made by substituting EXAMPLE 398F and diethylamine for EXAMPLE 35A and isopropylamine, respectively, in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.96 (m, 1H), 11.28 (m, 1H), 10.30 (m, 1H), 8.11 (m, 1H), 7.94 (s, 1H), 7.81 (d, 1H), 7.76 (d, 2H), 7.53 (m, 4H), 7.28 (m, 7H), 6.93 (m, 3H), 6.06 (m, 1H), 4.33 (m, 2H), 4.02 (m, 1H), 3.87 (m, 2H), 3.24 (m, 4H), 3.14 (m, 2H), 3.04 (m, 4H), 2.88 (m, 4H), 2.13 (m, 2H), 1.17 (m, 6H).

EXAMPLE 404

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1202] This example was made by substituting 2,5-dimethylpyrrolidine for isopropylamine, in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (m, 1H), 11.41 (m, 1H), 10.55 (m, 1H), 9.88 (m, 1H), 8.54 (s, 1H), 8.31 (d, 1H), 8.14 (m, 1H), 7.86 (dd, 1H), 7.77 (d, 2H), 7.53 (m, 4H), 7.24 (m, 8H), 6.93 (d, 2H), 4.33 (m, 2H), 3.88 (m, 2H), 3.26 (m, 7H), 2.83 (d, 2H), 2.16 (m, 4H), 1.65 (m, 2H), 1.36 (m, 6H).

EXAMPLE 405

4-(((1R)-3-amino-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(trifluoromethyl)benzenesulfonamide

[1203] This example was made by substituting EXAMPLE 398F and 7M NH_3 in methanol for EXAMPLE 35A and isopropylamine, respectively, in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (s, 1H), 7.87 (d, 1H), 7.72 (d, 2H), 7.51 (dd, 1H), 7.29 (m, 7H), 6.77 (m, 2H), 6.69 (m, 1H), 4.40 (m, 1H), 3.87 (m, 2H), 3.38 (m, 4H), 3.12 (m, 4H), 2.84 (t, 2H), 2.40 (m, 2H), 1.99 (m, 2H).

EXAMPLE 406A

[1204] This example was made by substituting 4-bromo-2-trifluoromethylbenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 406B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-(trifluoromethyl)benzenesulfonamide

[1205] This example was made by substituting EXAMPLE 406A for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, 1H), 7.79 (d, 2H), 7.48 (dd, 1H), 7.26 (m, 11H), 6.78 (m, 3H), 6.56 (m, 2H), 3.64 (m, 2H), 3.12 (m, 5H), 3.06 (m, 2H), 2.80 (m, 4H), 2.36 (m, 6H), 2.01 (m, 2H), 1.74 (m, 2H).

EXAMPLE 407A

[1206] This example was made by substituting 4-bromo-3-fluorobenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 407B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-fluorobenzenesulfonamide

[1207] This example was made by substituting EXAMPLE 407A for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (d, 2H), 7.48 (dd, 1H), 7.42 (d, 1H), 7.25 (m, 12H), 6.77 (m, 2H), 6.44 (t, 1H), 5.90 (d, 1H), 3.63 (m, 2H), 3.10 (m, 9H), 2.79 (m, 4H), 2.36 (m, 6H), 1.98 (m, 1H), 1.87 (m, 1H).

EXAMPLE 408A

[1208] This example was made by substituting 4-bromo-2-trifluoromethoxybenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 408B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-(trifluoromethoxy)benzenesulfonamide

[1209] This example was made by substituting EXAMPLE 408A for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, 2H), 7.62 (d, 1H), 7.51 (d, 1H), 7.31 (m, 12H), 6.81 (m, 2H), 6.39 (m, 2H), 3.61 (m, 2H), 3.39 (m, 2H), 3.17 (m, 6H), 3.09 (m, 4H), 2.79 (m, 1H), 2.40 (m, 6H), 1.98 (m, 1H), 1.87 (m, 1H).

EXAMPLE 409A

[1210] This example was made by substituting 4-bromo-2,5-difluorobenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 409B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2,5-difluorobenzenesulfonamide

[1211] This example was made by substituting EXAMPLE 409A for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, 2H), 7.51 (d, 1H), 7.31 (m, 10H), 6.80 (d, 2H), 6.20 (m, 2H), 6.10 (m, 2H), 3.59 (m, 1H), 3.39 (m, 4H), 3.14 (m, 6H), 2.94 (m, 2H), 2.85 (m, 2H), 2.40 (m, 6H), 2.01 (m, 1H), 1.90 (m, 1H).

EXAMPLE 410A

[1212] This example was made by substituting 4-bromo-3-methylbenzenesulfonamide for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 410B

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-methylbenzenesulfonamide

[1213] This example was made by substituting EXAMPLE 410A for EXAMPLE 164B in EXAMPLE 164C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.72 (d, 2H), 7.51 (d, 1H), 7.29 (m, 10H), 6.83 (d, 2H), 6.34 (d, 2H), 5.75 (s, 2H), 5.52 (d, 1H), 3.72 (m, 1H), 3.39 (m, 2H), 3.15 (m, 8H), 2.64 (m, 2H), 2.54 (m, 2H), 2.40 (m, 6H), 2.05 (s, 3H), 1.98 (m 1H), 1.87 (m, 1H).

EXAMPLE 411

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1214] This example was made by substituting EXAMPLE 307C and EXAMPLE 29D for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (s, 1H), 8.14 (m, 1H), 7.81 (m, 1H), 7.71 (d, 2H), 7.25 (m, 7H), 6.94 (d, 1H), 6.77 (d, 2H), 4.11 (m, 1H), 3.58 (m, 2H), 3.19 (m, 6H), 2.76 (s, 2H), 2.22 (m, 8H), 1.66 (m, 4H), 1.19 (m, 12H), 0.89 (m, 4H).

EXAMPLE 412

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1215] This example was made by substituting (2R,5R)-(-)-trans-2,5-dimethylpyrrolidine, prepared as described in J. Org. Chem. 1999,64, 1979-1985, for isopropylamine in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.17 (m, 1H), 7.84 (dd, 1H), 7.72 (d, 2H), 7.51 (d, 1H), 7.27 (m, 8H), 6.99 (d, 1H), 6.79 (d, 2H), 4.14 (m, 2H), 3.88 (m, 2H), 3.74 (m, 1H), 3.38 (s, 2H), 3.28 (m, 6H), 2.87 (m, 2H), 2.40 (m, 6H), 2.09 (m, 4H), 1.24 (m, 4H).

EXAMPLE 413

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2S,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1216] This example was made by substituting (2S,5S)-(+)-trans-2,5-dimethylpyrrolidine, prepared as described in J. Org. Chem. 1999,64, 1979-1985, for isopropylamine in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, 1H), 8.17 (m, 1H), 7.84 (dd, 1H), 7.72 (d, 2H), 7.51 (d, 1H), 7.27 (m, 8H), 6.94 (m, 1H), 6.79 (d, 2H), 4.11 (m, 2H), 3.88 (m, 2H), 3.74 (m, 1H), 3.38 (s, 2H), 3.27 (m, 6H), 2.87 (m, 2H), 2.40 (m, 6H), 2.09 (m, 4H), 1.24 (m; 4H).

EXAMPLE 414

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1217] This example was made by substituting (2S,5R)-cis-2,5-dimethylpyrrolidine, prepared as described in J. Org. Chem. 1999,64, 1979-1985, for isopropylamine in EXAMPLE 35B. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, 1H), 8.16 (m, 1H), 7.83 (dd, 1H), 7.72 (d, 2H), 7.51 (d, 1H), 7.27 (m, 8H), 6.97 (m, 1H), 6.80 (d, 2H), 4.12 (m, 2H), 3.49 (m, 1H), 3.39 (s, 2H), 3.28 (m, 8H), 2.40 (m, 6H), 2.12 (m, 4H), 1.57 (m, 2H), 1.21 (m, 4H).

EXAMPLE 415A

[1218] A mixture of 4-bromo-3-(trifluoromethyl)benzenesulfonyl chloride (0.46 g), concentrated sulfuric acid (6 mL), and 90% nitric acid (3 mL) at 110°C were stirred for 18 hours, poured into ice water and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 415B

[1219] EXAMPLE 415A (0.5 g) in IPA (25 mL) and THF (25 mL) at -78°C was treated with 38% ammonium hydroxide (10 mL), stirred for 3 hours, acidified with 12M HCl, and concentrated. The concentrate was treated with ethyl acetate and water. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 25% ethyl acetate/hexane.

EXAMPLE 415C

[1220] A mixture of EXAMPLE 415B (0.235 g), EXAMPLE 164A (0.224 g) and DIEA (1 mL) in dimethylacetamide (10 mL) at 50°C was stirred for 18 hours, treated with ethyl acetate, washed with aqueous $NaHCO_3$, water, and brine, and dried ($MgSO_4$), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl

acetate/NH_3-saturated dichloromethane.

EXAMPLE 415D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide

[1221] This example was made by substituting EXAMPLE 415C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, 1H), 8.20 (d, 1H), 7.83 (dd, 1H), 7.75 (d, 2H), 7.51 (dd, 1H), 7.37 (m, 8H), 7.06 (d, 2H), 6.79 (d, 2H), 6.50 (m, 1H), 3.39 (s, 2H), 3.29 (m 1H), 3.05 (m, 7H), 2.63 (m, 4H), 2.40 (m, 6H), 2.07 (m, 2H).

EXAMPLE 416

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide

[1222] This example was made by substituting EXAMPLE 415C and EXAMPLE 307C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (d, 1H), 8.10 (d, 1H), 7.65 (d, 2H), 7.27 (d, 2H), 7.04 (m, 8H), 6.68 (d, 2H), 6.44 (m, 1H), 3.04 (m, 4H), 2.82 (m, 1H), 2.69 (m, 2H), 2.41 (m, 6H), 2.20 (m, 4H), 2.08 (m, 4H), 1.98 (m, 2H), 1.56 (m, 4H).

EXAMPLE 417

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohepten-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-5-(trifluoromethyl)benzenesulfonamide

[1223] This example was made by substituting EXAMPLE 415C and EXAMPLE 318C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (d, 1H), 7.98 (d, 1H), 7.52 (d, 2H), 7.15 (d, 2H), 6.94 (m, 8H), 6.56 (d, 2H), 6.42 (m, 1H), 2.90 (m, 4H), 2.69 (m, 1H), 2.56 (m, 2H), 2.29 (m, 6H), 2.19 (m, 4H), 2.10 (m, 4H), 1.82 (m, 1H), 1.74 (m, 1H), 1.56 (m, 4H), 1.48 (m, 2H), 1.32 (m, 4H).

EXAMPLE 418A

[1224] 3-Fluoro-4-nitrobenzenesulfonyl chloride (1 g) in IPA (50 mL) at -15°C was treated with 38% NH_4OH (10 mL), stirred for 18 hours and concentrated. The concentrate was partitioned between ethyl acetate and water. The water layer was extracted with ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 418B

[1225] This example was made by substituting EXAMPLE 418A and EXAMPLE 164A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 21C, respectively, in EXAMPLE 21D.

EXAMPLE 418C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-4-nitrobenzenesulfonamide

[1226] This example was made by substituting EXAMPLE 418B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, 1H), 7.95 (d, 2H), 7.60 (s, 1H), 7.51 (dd, 1H), 7.37 (m, 4H), 7.30 (d, 4H), 7.24 (dd, 1H), 7.14 (t, 2H), 7.08 (t, 1H), 7.02 (dd, 1H), 6.79 (d, 2H), 4.13 (m, 1H), 3.49 (dd, 1H), 3.39 (d, 2H), 3.36 (dd, 1H), 3.13 (m, 4H), 3.04 (m, 2H), 2.63 (m, 4H), 2.40 (m, 6H), 2.10 (m, 2H).

EXAMPLE 419A

[1227] This example was made by substituting 4-bromo-3,5-difluorobenzenesulfonyl chloride for 3-fluoro-4-nitrobenzenesulfonyl chloride in EXAMPLE 418A.

EXAMPLE 419B

[1228] This example was made by substituting EXAMPLE 419A for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.

EXAMPLE 419C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3,5-difluorobenzenesulfonamide

[1229] This example was made by substituting EXAMPLE 419B for EXAMPLE 164B in EXAMPLE 164C.
^{1}H NMR (500 MHz, DMSO-d_6) δ 12.10 (m, 1H), 11.43 (m, 1H), 10.48 (m, 1H), 8.55 (m, 1H), 8.14 (m, 2H), 7.77 (m, 2H), 7.33 (m, 12H), 6.93 (m, 2H), 6.03 (d, 2H), 4.34 (m 1H), 3.88 (m, 2H), 3.36 (m, 4H), 3.13 (m, 2H), 2.84 (m, 2H), 2.70 (m, 6H), 2.08 (m, 2H).

EXAMPLE 420A

[1230] A mixture of 2-chloro-3-nitrobenzoic acid (5 g) and chlorosulfonic acid (30 mL) at 150°C was stirred for 72 hours, treated with ice, and extracted ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate in 1:1 IPA/THF (200 mL) at -78°C was treated with 38% ammonium hydroxide (30 mL), stirred for 2 hours, acidified with 12M HCl, and concentrated. The concentrate was treated with water and ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 420B

[1231] EXAMPLE 420A (4.5 g) in methanol (300 mL) was treated with concentrated sulfuric acid (3 mL), stirred at reflux for 18 hours, and concentrated. The concentrate was treated with water and ethyl acetate. The extract was washed with water and brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 20% ethyl acetate/hexane.

EXAMPLE 420C

[1232] This example was made by substituting EXAMPLE 420B and EXAMPLE 164A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 21C, respectively, in EXAMPLE 21D.

EXAMPLE 420D

methyl 5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoate

[1233] This example was made by substituting EXAMPLE 420C and EXAMPLE 307C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.34 (s, 1H), 8.28 (d, 1H), 7.72 (d, 2H), 7.36 (d, 2H), 7.13 (m, 7H), 6.76 (d, 2H), 3.80 (s, 3H), 3.10 (m, 4H), 2.75 (m, 2H), 2.27 (m, 4H), 2.18 (m, 6H), 1.99 (m, 2H), 1.88 (m, 2H), 1.65 (m, 4H).

EXAMPLE 421

5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid

[1234] This example was made by substituting EXAMPLE 420C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D.
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (s, 1H), 8.20 (d, 1H), 7.66 (d, 2H), 7.43 (d, 2H), 7.16 (m, 11H), 6.71 (d, 2H), 3.74

(s, 3H), 3.05 (m, 6H), 2.82 (m, 2H), 2.49 (m, 6H), 2.32 (m, 4H), 1.95 (m, 2H), 1.85 (m, 2H).

EXAMPLE 422

5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid

[1235] EXAMPLE 421 (60 mg) in THF (1 mL), methanol (1 mL), and water (1 mL) was treated with lithium hydroxide monohydrate (10 mg), stirred at 25°C for 18 hours, and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm × 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.55 (m, 1H), 9.13 (m, 1H), 8.46 (s, 1H), 8.33 (s, 1H), 7.79 (d, 2H), 7.72 (m, 1H), 7.52 (m, 4H), 7.49 (m, 2H), 7.33 (m, 2H), 7.09 (m, 4H), 6.99 (m, 2H), 6.93 (d, 2H), 4.21 (m, 1H), 3.17 (m, 6H), 2.93 (m, 2H), 2.79 (m, 6H), 2.12 (m, 2H), 2.05 (m, 2H).

EXAMPLE 423

5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzoic acid

[1236] This example was made by substituting EXAMPLE 420D for EXAMPLE 421 in EXAMPLE 422. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.57 (m, 1H), 9.21 (m, 1H), 8.47 (s, 1H), 8.33 (s, 1H), 7.80 (d, 2H), 7.40 (m, 4H), 7.15 (d, 2H), 7.09 (m, 4H), 7.01 (m, 2H), 6.95 (d, 2H), 3.17 (m, 6H), 2.79 (m, 6H), 2.26 (m, 4H), 2.21 (m, 4H), 2.14 (m, 2H), 2.03 (m, 2H), 1.70 (m, 4H).

EXAMPLE 424

5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-l-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzamide

[1237] EXAMPLE 420D (100 mg) in 7M NH_3 in methanol at 70°C was stirred for 48 hours in a sealed vial, and concentrated. The concentrate was purified by high pressure liquid chromatography on a Waters Symmetry C_8 column (25 mm × 100 mm, 7μm particle size) with 10-100% acetonitrile/0.1% aqueous TFA over 8 minutes at a flow rate of 40 mL/minute. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.46 (m, 1H), 8.52 (m, 1H), 8.45 (d, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.79 (d, 2H), 7.41 (m, 4H), 7.16 (d, 2H), 7.13 (m, 4H), 6.96 (d, 2H), 3.90 (m, 1H), 3.59 (m, 2H), 3.35 (m, 4H), 3.27 (m, 4H), 3.17 (m, 6H), 2.77 (m, 6H), 2.26 (m, 4H), 2.21 (m, 4H), 2.10 (m, 2H), 1.71 (m, 4H).

EXAMPLE 425

5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzamide

[1238] This example was made by substituting EXAMPLE 421 for EXAMPLE 420D in EXAMPLE 424. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.42 (m, 1H), 8.52 (m, 1H), 8.46 (d, 1H), 7.99 (s, 1H), 7.87 (s, 1H), 7.78 (d, 2H), 7.53 (m, 4H), 7.41 (d, 2H), 7.34 (m, 1H), 7.14 (m, 4H), 6.94 (d, 2H), 3.91 (m, 1H), 3.36 (m, 4H), 3.28 (m, 4H), 3.16 (m, 6H), 2.77 (m, 6H), 2.11 (m, 2H).

EXAMPLE 426A

[1239] 2-Fluoro-3-(trifluoromethyl)benzoic acid (5 g) in concentrated sulfuric acid (50 mL) at 0°C was treated with urea nitrate, prepared as described in Textbook of Practical Organic Chemistry; 1971, page 442, (5 g), stirred for 30 minutes and at 25°C for 12 hours, poured onto crushed ice and extracted with ethyl acetate. The extract was washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate in methanol (300 mL) and concentrated sulfuric acid (3 mL) was refluxed for 18 hours and concentrated. The concentrate was treated with water and ethyl acetate, and the organic layer was washed with water and brine, and dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 426B

[1240] EXAMPLE 426A (6 g) and 10% palladium on carbon (0.6 g) in ethyl acetate (200 mL) at 25°C were shaken

under H_2 (60 psi) for 2 hours, filtered and concentrated.

EXAMPLE 426C

[1241] This example was made by substituting EXAMPLE 426B for EXAMPLE 848090A in EXAMPLE 848090B.

EXAMPLE 426D

[1242] This example was made by substituting EXAMPLE 426C and EXAMPLE 164A for 4-fluoro-3-nitrobenzenesulfonamide and EXAMPLE 21C, respectively, in EXAMPLE 21D.

EXANPLE 426E

methyl 5-(((4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate

[1243] This example was made by substituting EXAMPLE 426D and EXAMPLE 307C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, 1H), 8.16 (d, 1H), 7.72 (d, 2H), 7.36 (d, 2H), 7.30 (m, 1H), 7.20 (d, 2H), 7.12 (m, 4H), 6.77 (d, 2H), 3.81 (s, 3H), 3.62 (m, 1H), 3.12 (m, 8H), 2.95 (m, 2H), 2.77 (m, 2H), 2.61 (m, 6H), 2.28 (m, 4H), 2.18 (m, 4H), 2.10 (m, 2H), 1.91 (m, 2H), 1.66 (m, 4H).

EXAMPLE 427

methyl 5-(((4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate

[1244] This example was made by substituting EXAMPLE 426D and EXAMPLE 312D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, 1H), 8.15 (d, 1H), 7.72 (d, 2H), 7.40 (d, 2H), 7.30 (m, 1H), 7.20 (m, 4H), 7.12 (m, 2H), 6.77 (d, 2H), 4.16 (s, 2H), 3.81 (s, 3H), 3.79 (t, 2H), 3.62 (m, 1H), 3.12 (m, 8H), 2.95 (m, 2H), 2.88 (m, 4H), 2.60 (m, 6H), 2.30 (m, 4H), 2.05 (m, 2H), 1.91 (m, 2H).

EXAMPLE 428

methyl 5-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-(trifluoromethyl)benzoate

[1245] This example was made by substituting EXAMPLE 426D for 4-(((1R)-3-(dimethylamino)-l-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, 1H), 8.16 (d, 1H), 7.73 (d, 2H), 7.50 (d, 2H), 7.47 (m, 4H), 7.24 (m, 6H), 6.79 (d, 2H), 3.81 (s, 3H), 3.61 (m, 1H), 3.38 (s, 2H), 3.12 (m, 8H), 2.95 (m, 2H), 2.61 (m, 6H), 2.40 (m, 4H), 2.10 (m, 2H), 1.91 (m, 2H).

EXAMPLE 429A

[1246] This example was made by substituting Fmoc-D-Glu(O-tert-butyl)-OH for Fmoc-D-Asp(O-tert-butyl)-OH in EXAMPLE 27A.

EXAMPLE 429B

[1247] This example was made by substituting EXAMPLE 429A for EXAMPLE 27A in EXAMPLE 27B.

EXAMPLE 429C

[1248] This example was made by substituting EXAMPLE 429B for EXAMPLE 27B in EXAMPLE 29A.

EXAMPLE 429D

[1249] This example was made by substituting EXAMPLE 429C and (2S,5R)-cis-2,5-dimethylpyrrolidine, prepared as described in J. Org. Chem. 1999,64, 1979-1985, for EXAMPLE 29A and diisopropylamine, respectively, in EXAMPLE 29B.

EXAMPLE 429E

[1250] This example was made by substituting EXAMPLE 429D for EXAMPLE 27B in EXAMPLE 398B.

EXAMPLE 429F

[1251] This example was made by substituting EXAMPLE 429E for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 429G

[1252] This example was made by substituting EXAMPLE 429F for EXAMPLE 21C in EXAMPLE 21D.

EXAMPLE 429H

N-(4-(4-((2-(4-chlorophenyl)-1-cyclohexen-1-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[1253] This example was made by substituting EXAMPLE 429G and EXAMPLE 307C for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.17 (m, 1H), 9.01 (m, 1H), 8.53 (d, 1H), 8.32 (d, 1H), 7.87 (dd, 1H), 7.79 (d, 2H), 7.41 (d, 2H), 7.18 (m, 6H), 6.96 (d, 2H), 4.18 (m, 1H), 3.90 (m, 2H), 3.60 (m, 2H), 3.09 (m, 2H), 2.78 (m, 2H), 2.26 (m, 4H), 2.09 (m, 2H), 1.68 (m, 8H), 1.28 (d, 6H).

EXAMPLE 430

N-(4-(4-((4-(4-chlorophenyl)-5,6-dihydro-2H-pyran-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-4-((2R,5S)-2,5-dimethylpyrrolidin-1-yl)-1-((phenylsulfanyl)methyl)butyl)amino)-3-nitrobenzenesulfonamide

[1254] This example was made by substituting EXAMPLE 429G and EXAMPLE 312D for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide and EXAMPLE 2C, respectively, in EXAMPLE 2D. ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (m, 1H), 10.54 (m, 1H), 9.00 (m, 1H), 8.53 (d, 1H), 8.32 (d, 1H), 7.88 (dd, 1H), 7.78 (d, 2H), 7.45 (d, 2H), 7.18 (m, 6H), 6.96 (d, 2H), 4.38 (s, 2H), 4.18 (m, 1H), 3.84 (t, 2H), 3.66 (m, 2H), 3.09 (m, 2H), 2.75 (m, 2H), 2.46 (m, 4H), 2.09 (m, 2H), 1.68 (m, 8H), 1.28 (d, 6H).

EXAMPLE 431

tert-butyl 3-((4-(4-((((4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrophenyl)sulfonyl)amino)carbonyl)phenyl)piperazin-1-yl)carbonyl)phenylcarbamate

[1255] This example was made by substituting 2-tert-butoxycarbonylaminobenzoyl chloride for 2-bromobenzoyl chloride in EXAMPLE 106B. ^{1}H NMR (500MHz, DMSO-d_6) δ 9.48 (s, 1H), 9.28 (brs, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 7.88 (dd, 1H), 7.77 (d, 2H), 7.24 (d, 2H), 7.16 (dd, 2H), 7.12 (d, 1H), 6.96 (d, 2H), 6.63 (d, 1H), 6.58 (s, 1H), 6.50 (d, 1H), 4.18 (m, 1H), 3.40 (m, 4H), 3.35 (m, 2H), 3.20-3.08 (m, 4H), 2.73 (s, 6H), 2.54 (s, 2H), 2.14 (m, 2H), 1.48 (s, 9H).

EXAMPLE 432

N-(4-(4-(3-(dimethylamino)benzoyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1256] This example was made by substituting 2-dimethylaminobenzoyl chloride for 2-bromobenzoyl chloride in EXAMPLE 106B. ^{1}H NMR (500MHz, DMSO-d_6) δ 9.26 (br s, 1H), 8.55 (d, 1H), 8.28 (d, 1H), 7.87 (dd, 1H), 7.77 (d, 2H), 7.23 (d, 2H), 7.15 (dd, 2H), 7.11 (d, 1H), 6.96 (d, 2H), 6.79 (d, 1H), 6.69 (s, 1H), 6.65 (d, 1H), 4.17 (m, 1H), 3.40 (m,

4H), 3.35 (m, 2H), 3.15 (m, 4H), 2.91 (s, 6H), 2.74 (s, 6H), 2.54 (s, 2H), 2.14 (m, 2H).

EXAMPLE 433A

[1257] This example was made by substituting (2S,4R)-3-((benzyloxy)carbonyl)-4-methyl-2-phenyl-1,3-oxazolidin-5-one, (prepared as described in Helv. Chim. Acta 1991, for (2R,4S)-3-((benzyloxy)carbonyl)-4-methyl-2-phenyl-1,3-oxazolidin-5-one in EXAMPLE 25A.

EXAMPLE 433B

[1258] This example was made by substituting EXAMPLE 433A for EXAMPLE 25A in EXAMPLE 25B.

EXAMPLE 433C

[1259] This example was made by substituting EXAMPLE 433B for EXAMPLE 25B in EXAMPLE 25C.

EXAMPLE 433D

[1260] This example was made by substituting EXAMPLE 433C for EXAMPLE 18A in EXAMPLE 18B.

EXAMPLE 433E

[1261] This example was made by substituting EXAMPLE 433D for EXAMPLE 25D in EXAMPLE 25E.

EXAMPLE 433F

[1262] This example was made by substituting EXAMPLE 433E for EXAMPLE 25E in EXAMPLE 25F.

EXAMPLE 433G

[1263] This example was made by substituting EXAMPLE 433F for EXAMPLE 18B in EXAMPLE 18C.

EXAMPLE 433H

[1264] This example was made by substituting EXAMPLE 433G for EXAMPLE 25G in EXAMPLE 25H.

EXAMPLE 433I

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1265] This example was made by substituting EXAMPLE 433H for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.51 (d, 1H), 8.31 (s, 1H), 7.92 (dd, 1H), 7.81 (d, 2H), 7.60 (d, 1H), 7.47 (m, 4H), 7.42 (m, 3H), 7.32 (m, 4H), 7.16 (dd, 2H), 7.08 (dd, 1H), 6.86 (d, 2H), 4.25 (m, 1H), 3.77 (d, 2H), 3.45 (d, 1H), 3.21 (m, 4H), 2.95 (m, 1H), 2.67 (s, 6H), 2.54 (m, 1H), 2.45 (m, 4H), 2.27 (m, 1H), 1.59 (s, 3H).

EXAMPLE 434

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1266] This example was made by substituting EXAMPLE 25H for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.20 (br s, 1H), 8.48 (d, 1H), 8.26 (s, 1H), 7.87 (dd, 1H), 7.78 (d, 2H), 7.56 (d, 1H), 7.42 (m, 4H), 7.38 (m, 3H), 7.29 (d, 1H), 7.25 (m, 3H), 7.05 (dd, 2H), 6.97 (dd, 1H), 6.83 (d, 2H), 3.74 (m, 1H), 3.45 (s, 2H), 3.39 (d, 1H), 3.28 (m, 1H), 3.20 (m, 4H), 3.16 (m, 1H), 2.97 (m, 1H), 2.67 (s, 6H), 2.54 (m, 1H), 2.40 (m, 4H), 2.25 (m, 1H), 1.54 (s, 3H).

EXAMPLE 435A

[1267] 2-fluorobenzonitrile (0.325 mL) in isoindoline/NMP (1 mL/2 mL) at 180°C was stirred for 10 minutes in a microwave reactor, poured into diethyl ether (50 mL) and washed with 1M HCl and brine. The solution was dried (Na_2SO_4), filtered, and concentrated.

EXAMPLE 435B

[1268] EXAMPLE 435A (200 mg) in toluene (5 mL) at 25°C was treated with 1M DIBAL in dichloromethane (1.1 mL), stirred for 30 minutes, treated with methanol (3 mL), poured into 1M HCl (50 mL), and extracted with ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 10% ethyl acetate/hexanes.

EXAMPLE 435C

N-(4-(4-(2-(1,3-dihydro-2H-isoindol-2-yl)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1269] This example was made by substituting EXAMPLE 435B for EXAMPLE 130D in EXAMPLE 130E. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.05 (br s, 1H), 8.45 (d, 1H), 8.21 (d, 1H), 7.81 (dd, 1H), 7.73 (d, 2H), 7.34 (m, 4H), 7.23 (m, 4H), 7.18 (m, 2H), 7.07 (m, 1H), 6.89 (m, 2H), 6.81 (d, 2H), 4.62 (AB quartet, 4H), 4.09 (m, 1H), 3.62 (s, 1H), 3.34 (m, 2H), 3.28 (m, 1H), 3.20 (m, 2H), 2.91 (dd, 2H), 2.84 (m, 1H), 2.67 (s, 6H), 2.55 (m, 4H), 2.09 (m, 1H), 2.02 (m, 1H), 1.71 (m, 1H).

EXAMPLE 436A

[1270] This example was made by substituting cyclohexylamine for isoindoline in EXAMPLE 435A.

EXAMPLE 436B

[1271] This example was made by substituting EXAMPLE 436A for EXAMPLE 435A in EXAMPLE 435B.

EXAMPLE 436C

N-(4-(4-(2-(cyclohexylamino)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1272] This example was made by substituting EXAMPLE 436B for 2-(methylsulfanyl)benzaldehyde in EXAMPLE 128E. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.70 (br s, 1H), 8.52 (d, 1H), 8.22 (d, 1H), 7.84 (dd, 1H), 7.76 (d, 2H), 7.26 (d, 2H), 7.19 (m, 2H), 7.11 (m, 2H), 6.97 (dd, 1H), 6.89 (d, 2H), 6.58 (d, 1H), 6.49 (m, 1H), 4.19 (m, 1H), 3.51 (m, 1H), 3.38 (d, 2H), 3.34 (m, 5H), 3.11 (m, 4H), 2.70 (s, 6H), 2.47 (m, 3H), 2.17 (m, 2H), 1.88 (m, 2H), 1.62 (m, 2H), 1.53 (m, 1H), 1.37 (m, 2H), 1.22 (m, 4H).

EXAMPLE 437A

[1273] This example was made by substituting isopropylamine for isoindoline in EXAMPLE 435A.

EXAMPLE 437B

[1274] This example was made by substituting EXAMPLE 437A for EXAMPLE 435A in EXAMPLE 435B.

EXAMPLE 437C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-(2-(isopropylamino)benzyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide

[1275] This example was made by substituting EXAMPLE 437B for 2-(methylsulfanyl)benzaldehyde in EXAMPLE 128E. ^{1}H NMR (400MHz, DMSO-d_6) δ 9.82 (br s, 1H), 8.52 (d, 1H), 8.22 (d, 1H), 7.84 (dd, 1H), 7.78 (d, 2H), 7.25 (d,

2H), 7.18 (m, 2H), 7.13 (m, 2H), 6.99 (m, 1H), 6.92 (d, 2H), 6.60 (d, 1H), 6.51 (dd, 1H), 4.21 (m, 1H), 3.49 (m, 3H), 3.39 (d, 2H), 3.31 (m, 5H), 3.11 (m, 4H), 3.08 (d, 2H), 2.71 (s, 6H), 2.51 (m, 1H), 2.16 (m, 2H), 1.14 (d, 6H).

EXAMPLE 438A

[1276] This example was made by substituting benzylamine for isoindoline in EXAMPLE 435A.

EXAMPLE 438B

[1277] This example was made by substituting EXAMPLE 438A for EXAMPLE 435A in EXAMPLE 435B.

EXAMPLE 438C

N-(4-(4-(2-(benzylamino)benzyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1278] This example was made by substituting EXAMPLE 438B for 2-(methylsulfanyl)benzaldehyde in EXAMPLE 128E. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.18 (br s, 1H), 8.52 (d, 1H), 8.25 (d, 1H), 7.84 (dd, 1H), 7.78 (d, 2H), 7.37 (d, 2H), 7.29 (dd, 2H), 7.24 (m, 2H), 7.19 (m, 2H), 7.12 (m, 3H), 7.07 (m, 1H), 6.95 (d, 2H), 6.56 (dd, 1H), 6.52 (d, 1H), 4.35 (s, 2H), 4.25 (m, 1H), 3.39 (d, 2H), 3.35 (m, 4H), 3.18 (m, 1H), 3.05 (m, 8H), 2.68 (s, 6H), 2.51 (m, 1H), 2.19 (m, 2H).

EXAMPLE 439A

[1279] This example was made by substituting piperidine for isoindoline in EXAMPLE 435A.

EXAMPLE 439B

[1280] This example was made by substituting EXAMPLE 439A for EXAMPLE 435A in EXAMPLE 435B.

EXAMPLE 439C

4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4-(2-(piperidin-1-yl)benzyl)piperazin-1-yl)benzoyl)benzenesulfonamide

[1281] This example was made by substituting EXAMPLE 439B for 2-(methylsulfanyl)benzaldehyde in EXAMPLE 128E. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.49 (d, 1H), 8.19 (m, 1H), 7.82 (dd, 1H), 7.75 (d, 2H), 7.41 (m, 1H), 7.35 (m, 1H), 7.30 (d, 2H), 7.22 (m, 3H), 7.15 (m, 1H), 7.02 (m, 2H), 6.87 (d, 1H), 4.12 (m, 1H), 3.60 (m, 2H), 3.42 (m, 1H), 3.37 (d, 2H), 3.31 (m, 5H), 3.22 (m, 2H), 3.08 (m, 2H), 2.82 (m, 4H), 2.69 (s, 6H), 2.59 (m, 2H), 2.10 (m, 2H), 1.65 (m, 4H), 1.51 (m, 2H), 1.21 (m, 4H).

EXAMPLE 440

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1282] This example was made by substituting 4-cyclohexylamino-3-nitro-benzenesulfonamide, prepared as described in WO02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.90 (brs, 1H), 8.61 (d, 1H), 8.60 (dd, 1H), 7.94 (dd, 1H), 7.74 (d, 2H), 7.59 (d, 1H), 7.41 (dd, 2H), 7.38 (m, 4H), 7.25 (d, 1H), 7.22 (d, 1H), 6.89 (d, 2H), 3.58 (m, 2H), 3.25 (m, 3H), 2.47 (m, 4H), 1.85 (d, 2H), 1.69 (m, 3H), 1.61 (m, 2H), 1.19 (m, 4H), 0.99 (m, 2H).

EXAMPLE 441

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-4-((cyclohexylmethyl)amino)-3-nitrobenzenesulfonamide

[1283] This example was made by substituting 4-cyclohexylmethylamino-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 11.90 (br s, 1H), 8.70 (d, 1H), 8.36 (dd, 1H), 7.99 (dd, 1H),

7.78 (d, 2H), 7.50 (d, 1H), 7.45 (dd, 2H), 7.42 (m, 4H), 7.35 (d, 1H), 7.32 (d, 1H), 6.94 (d, 2H), 3.76 (m, 2H), 3.69 (m, 2H), 3.38 (m, 1H), 2.58 (m, 4H), 1.99 (d, 2H), 1.74 (m, 3H), 1.62 (m, 2H), 1.45 (m, 6H), 1.29 (m, 2H).

EXAMPLE 442

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1284] This example was prepared by substituting EXAMPLE 90C and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (400MHz, DMSO-d_6) δ 11.43 (br s, 1H), 8.54 (d, 1H), 8.38 (d, 1H), 7.83 (dd, 1H), 7.79 (d, 2H), 7.41 (dd, 2H), 7.35 (m, 2H), 7.28 (m, 6H), 7.17 (m, 4H), 6.80 (d, 2H), 4.19 (m, 1H), 3.62 (m, 4H), 3.39 (m, 2H), 3.30 (m, 2H), 3.02 (s, 3H), 2.90 (s, 2H), 2.85 (dd, 2H), 2.65 (m, 6H), 2.08 (m, 1H), 1.98 (m, 1H), 1.47 (d, 2H), 1.18 (m, 2H).

EXAMPLE 443

N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)-4-methoxypiperidin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide

[1285] This example was prepared by substituting EXAMPLE 90C and 3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 2D.
^{1}H NMR (400MHz, DMSO-d_6) δ 11.95 (br s, 1H), 8.75 (dd, 1H), 8.60 (d, 1H), 7.91 (dd, 1H), 7.79 (d, 2H), 7.41 (dd, 2H), 7.36 (m, 3H), 7.28 (m, 6H), 7.17 (m, 3H), 6.80 (d, 2H), 3:66 (m, 2H), 3.39 (m, 2H), 3.29 (m, 2H), 3.02 (s, 3H), 2.90 (s, 2H), 2.86 (dd, 2H), 1.45 (m, 2H), 1.18 (m, 2H).

EXAMPLE 444A

[1286] 4-chloro-3-(trifluoromethyl)benzenesulfonyl chloride (5 g) in THF (100 mL) was treated with saturated NH_4OH at 0°C, stirred for 30 minutes and concentrated. The concentrate in ethyl acetate was washed with water and brine, and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 30% ethyl acetate in hexanes.

EXAMPLE 444B

[1287] A mixture of EXAMPLE 444A (1.5 g) and 2-(phenylsulfanyl)ethanamine (1.06 g) in DMSO (17 mL) was treated with TEA (0.97 mL), heated at 145°C for 18 hours, cooled to 25°C, poured into ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 50% ethyl acetate/hexanes.

EXAMPLE 444C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-l-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1288] This example was made by substituting EXAMPLE 444B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.88 (d, 1H), 7.77 (d, 1H), 7.73 (dd, 2H), 7.51 (d, 1H), 7.49 (s, 4H), 7.40 (dd, 2H), 7.35 (m, 4H), 7.21 (m, 2H), 6.78 (d, 2H), 6.70 (d, 1H), 3.41 (m, 2H), 3.39 (s, 1H), 3.16 (m, 2H), 3.13 (m, 4H), 2.50 (s, 1H), 2.40 (m, 4H).

EXAMPLE 445A

[1289] This example was made by substituting EXAMPLE 444A for 4-fluoro-3-nitrobenzenesulfonamide, prepared as described in WO02/24636, in EXAMPLE 20D.

EXAMPLE 445B

[1290] This example was made by substituting EXAMPLE 445A for EXAMPLE 18E in EXAMPLE 18F.

EXAMPLE 445C

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propyl)amino)-3-(trifluoromethyl)benzenesulfonamide

[1291] This example was made by substituting EXAMPLE 445B for 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide in EXAMPLE 2D. ^{1}H NMR (500MHz, DMSO-d_6) δ 10.90 (br s, 1H), 7.94 (d, 1H), 7.79 (d, 1H), 7.74 (d, 2H), 7.53 (d, 1H), 7.47 (s, 4H), 7.38 (m, 2H), 7.32 (m, 2H), 7.26 (m, 3H), 7.19 (m, 1H), 6.87 (d, 3H), 3.99 (m, 1H), 3.42 (s, 2H), 3.29 (m, 2H), 3.17 (m, 4H), 3.02 (m, 4H), 2.40 (m, 4H), 2.16 (m, 2H), 1.89 (m, 4H), 1.28 (m, 2H).

EXAMPLE 446A

[1292] 4-chloronicotinic acid (5 g) in 1:1 methanol/ethyl acetate (200 mL) was treated with 2M trimethylsilyldiazomethane (25 mL) and concentrated.

EXAMPLE 446B

[1293] A mixture of EXAMPLE 446A (4.88 g), 4-chlorobenzeneboronic acid (5.15 g), KF (5.45 g), $Pd_2(dba)_3$ (260 mg), and tri-tert-butylphosphine in THF (80 mL) at 25°C was stirred for 3 days, filtered and concentrated. The concentrate was flash chromatographed on silica gel with 20% ethyl acetate/hexanes.

EXAMPLE 446C

[1294] EXAMPLE 446B (3.4 g) in THF (50 mL) at 0°C was treated with 1M $LiAlH_4$ in THF (14 mL), stirred at 25°C for 1 hour, quenched with water (5 mL) and 1M NaOH (20 mL), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with ethyl acetate.

EXAMPLE 446D

[1295] EXAMPLE 446C (530 mg) in acetonitrile (15 mL) at 0°C was treated with pyridine (0.315 mL) and dibromotriphenylphosphorane (1.32 g), stirred at 25°C for 1 hour, and poured into saturated Na_2CO_3 (100 mL) and ethyl acetate. The extract was washed with brine and dried (Na_2SO_4), filtered, and concentrated. The concentrate was flash chromatographed on silica gel with 1:1 ethyl acetate/hexanes.

EXAMPLE 446E

[1296] This example was made by substituting EXAMPLE 446D for 2-bromobenzyl bromide in EXAMPLE 2A.

EXAMPLE 446F

[1297] This example was made by substituting EXAMPLE 446E for EXAMPLE 1B in EXAMPLE 1C.

EXAMPLE 446G

N-(4-(4-((4-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1298] This example was made by substituting EXAMPLE 446F for EXAMPLE 1C in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.55 (d, 1H), 8.52 (d, 1H), 8.23 (d, 1H), 7.85 (dd, 1H), 7.74 (d, 2H), 7.58 (d, 2H), 7.54 (d, 2H), 7.31 (d, 1H), 7.26 (d, 1H), 7.17 (dd, 2H), 7.13 (d, 1H), 7.12 (m, 1H), 6.88 (d, 2H), 4.19 (m, 1H), 3.47 (s, 2H), 3.32 (m, 4H), 3.11 (m, 4H), 2.71 (s, 6H), 2.42 (m, 4H), 2.16 (m, 2H).

EXAMPLE 447

N-(4-(4-((4-(4-chlorophenyl)pyridin-3-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide

[1299] This example was made by substituting EXAMPLE 446F and 4-(((1R)-3-(4-morpholinyl)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide, prepared as described in WO 02/24636, for EXAMPLE 2C and 4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide, respectively, in EXAMPLE 20. ^{1}H NMR (500MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.56 (d, 1H), 8.52 (d, 1H), 8.34 (d, 1H), 7.83 (dd, 1H), 7.74 (d, 2H), 7.58 (d, 2H), 7.54 (d, 2H), 7.31 (d, 1H), 7.27 (d, 1H), 7.19 (dd, 2H), 7.13 (d, 1H), 7.11 (m, 1H), 6.88 (d, 2H), 4.19 (m, 1H), 3.63 (s, 4H), 3.22 (s, 4H), 3.08 (m, 4H), 2.75-2.55 (m, 6H), 2.42 (m, 4H), 2.10 (m, 1H), 1.98 (m, 1H).

EXAMPLE 448A

[1300] This example was made by substituting 2,6-difluorobenzotrifluoride for 1-fluorobenzotrifluoride in EXAMPLE 18D.

EXAMPLE 448B

[1301] This example was made by substituting EXAMPLE 448A for EXAMPLE 18D in EXAMPLE 18E.

EXAMPLE 448C

[1302] This example was made by substituting EXAMPLE 448B for EXAMPLE 18E in EXAMPLE 18F.

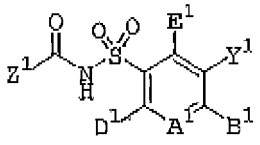
EXAMPLE 448D

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-2-fluoro-3-(trifluoromethyl)benzenesulfonamide

[1303] This example was made by substituting EXAMPLE 448C for EXAMPLE 1C in EXAMPLE 1D. ^{1}H NMR (500MHz, DMSO-d_6) δ 7.82 (d, 2H), 7.76 (dd, 1H), 7.64 (d, 1H), 7.54 (d, 2H), 7.51 (d, 2H), 7.44 (m, 2H), 7.40 (d, 2H), 7.35 (dd, 2H), 7.31 (d, 1H), 7.25 (dd, 1H), 6.93 (d, 2H), 6.74 (d, 1H), 4.02 (m, 1H), 3.55 (m, 4H), 3.35 (m, 2H), 3.18 (m, 2H), 3.06 (m, 2H), 2.74 (s, 6H), 2.52 (m, 4H), 2.21 (m, 2H).

Claims

1. A compound having formula (I)



(I),

or a therapeutically acceptable salt thereof, wherein

A^1 is $C(A^2)$;
A^2 is H, F, CN, C(O)OH, $C(O)NH_2$ or $C(O)OCH_3$;
B^1 is R^1, OR^1, NHR^1, $N(R^1)_2$ or $NR^1C(O)N(R^1)_2$;
D^1 is H, F, Cl or CF_3;
E^1 is H, F or Cl;
Y^1 is H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2, $C(O)NH_2$, or
B^1 and Y^1, together with the atoms to which they are attached, are imidazole or triazole;
R^1 is phenol, pyrrolyl, cyclopentyl, cyclohexyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothi-

opyranyl or R^5;
R^5 is C_1-alkyl, C_2-alkyl, C_3-alkyl, C_4-alkyl, C_5-alkyl or C_6-alkyl, each of which is unsubstituted or substituted with one or two or three independently selected C_4-spiroalkyl, C_5-spiroalkyl, R^7, OR^7, SR^7, SO_2R^7, NHR^7, $N(R7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, $NHC(O)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, OH, C(O)OH or NH_2 substituents;
R^7 is phenyl, furanyl, imidazolyl, pyridinyl, tetrazolyl, thiazolyl, thienyl, 1,3-benzoxazolyl, 1,3-benzodioxolyl, 1,3-benzothiazole, cyolopropyl, cyclobutyl, cyclohexyl, azetidinyl, morpholinyl, piperazinyl, piperidinyl, thiomorpholinyl, thiomorpholinyl sulfone 7-azabicyclo[2.2.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, 4,5-dihydio-1H-imidazoly] 2-oxa-5-azabicyclo [2.2.1] heptanyl, 1,4,5,6-tehahydropyrimidinyl or R^{11};
R^{11} is C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is unsubstituted or substituted with one or two or three independently selected R^{12}, OR^{12}, $N(R^{12})_2$, $C(O)N(R^{12})_2$, OH, C(O)OH, NH_2, CF_3, F, Cl, Br or I substituents;
R^{12} is 1,3-benzodioxolyl, pyridinyl, morpholinyl or C_1-alkyl;
Z^1 is phenyl or pyridinyl, each of which is substituted with cyclohexenyl, piperazinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl or octahydropyrrolo[3,4-c]pyrrolyl, each of which is substituted with CH_2R^{37}, $C(C_2$-spiroalkyl$)(R^{37})$ or $C(O)R^{37}$;
R^{37} is phenyl, naphthyl, imidazolyl, pyrazolyl, pyridinyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl or 3,6-dihydro-2H-pyranyl, each of which is substituted with R^{41}, NHR^{41}, $N(R^{41})_2$, $MHC(O)OR^{41}$ or SR^{41};
R^{41} is phenyl, naphthyl, cyclohexyl, morpholinyl, piperidinyl, thienyl, pyridinyl, quinolinyl, benzofuranyl, 1,3-benzodioxolyl, isoindolinyl, 1,3-oxazolidin-2-onyl or R^{45};
R^{45} is C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is substituted with phenyl; wherein the moieties represented by B^1 and Y^1 together are substituted with C_2-alkyl, C_3-alkyl or C_4-alkyl, each of which is substituted with one or two independently selected SR^{55} or $N(R^{55})_2$ substituents, wherein R^{55} is independently selected phenyl or C_1-alkyl;
the moieties represented by R^1 are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, SR^{50}, SO_2R^{50}, $CO(O)R^{50}$ or OCF_3 substituents, wherein R^{50} is phenyl, C_1-alkyl, C_2-alkyl, C_3-alkyl or C_4-alkyl;
the moieties represented by R^7 are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, $C(O)NHSO_2R^{50}$, $CO(O)R^{50}$, $C(O)R^{50}$, C(O)OH, C(O)NHOH, OH, NH_2, F, Cl, Br or I substituents, wherein R^{50} is phenyl, tetrazolyl or R^{54}, wherein R^{54} is C_1-alkyl, C_2-alkyl or C_3-alkyl, each of which is unsubstituted or substituted with phenyl;
the phenyl and pyridinyl moieties of Z^1 are further unsubstituted or substituted with one or two independently selected F, Br, Cl or I substituents;
the cyclohexenyl, piperazinyl, piperidinyl, 1,2,3,6-tetrahydropyridinyl and octahydropyrrolo [3,4-c]pyrrolyl moieties of Z^1 are further unsubstituted or substituted with OR^{54}, wherein R^{54} is C_1-alkyl or C_2-alkyl, each of which is unsubstituted or substituted with $N(C_1$-alkyl$)_2$, morpholinyl, piperidinyl or piperidinyl;
the moieties represented by R^{37} are further unsubstituted or substituted with one or two independently selected C_1-alkyl, F, Br, Cl or I substituents;

and

the moieties represented by R^{41} are unsubstituted or substituted with one or two independently selected R^{50}, OR^{50}, SR^{50}, $N(R^{50})_2$, SO_2R^{50}, CN, OCF_3, F, Cl, Br or I substituents, wherein R^{50} is phenyl or R^{54}, wherein R^{54} is C_1-alkyl, C_2-alkyl or C_3-alkyl, each of which is unsubstituted or substituted with $N(C_1$-alkyl$)_2$ or morpholinyl.

2. A pharmaceutical composition comprising compounds of claim 1 or their pharmaceutically acceptable salts.

3. Compounds of claim 1 or their pharmaceutically acceptable salts for use in medicine.

4. A composition for use in the treatment of bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, Melanoma, myelogenous leukemia, myolama, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer, said composition comprising an excipient and a therapeutically effective amount of the compound or therapeutically acceptable salt of claim 1.

5. Use of a compound or therapeutically acceptable salt of claim 1 for manufacturing a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal

cancer, esophageal cancer hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound or therapeutically acceptable salt of claim 1 is adapted for administration to a patient in a therapeutically effective amount.

6. Use according to claim 5, wherein the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl) -propyl) amino)-3-nitrobenzenesulfonamide.

7. Use according to claim 5 wherein the compound or therapeutically acceptable salt of claim 1, and one additional therapeutic agent or more than one additional therapeutic agent, are employed for manufacturing a medicament for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound or therapeutically acceptable salt of claim 1, and the one additional therapeutic agent or the more than one additional therapeutic agent, are adapted for administration to a patient in a therapeutically effective amount.

8. Use according to claim 7 wherein the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenssulfonamide.

9. The compound of claim 1 wherein the compound is N-(4-(4-(4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide or a therapeutically acceptable salt thereof.

10. The compound of claim 1 where the compound is selected from:

N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)methyl)-3-(pyrrolidin-1-yl)propyl)amino)benzenesulfonamide,
N-C4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(1,3-thiazol-2-ylsulfanyl)ethyl)aminoa)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(1R)-3-(dimethylalnino)-1-((1,3-thiazol-2-ylsulfonyl)methyl)propyl)amino)-3--nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethyl)amin)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)butanoic acid,
(3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-4-(phenylsulfanyl)butanamide,
N-(4-(4-((4'-chloro[1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfanamide,
4-(((1R)-3-(azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenysulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)pipeyazin-1-yl)-benzoyl)-4-(((1R)-3-hydroxy-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((3'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((3'-chloro(1,1-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-(phenylsul-

fanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(-4-(4-((2'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl) cyclopentyl)amino)benzenesulfonamide,
N-(4-(4-((4'-fluoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
N-(4-(4'((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzensulfonamide,
N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((3',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
3-nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzenesulfonamide,
4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-N-(4-(4'((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl) benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-(((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfonyl)ethyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2',4'-dichloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N'-(4-(4-((4'-chloro-2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethyl amino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((2',4'-diffuoro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzenesulfonamide,
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phei)ylsulfonyl)ethyl)amino)benzenesulfonamide,
N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzenesulfonamide, and
N-(4-(4-((1,1'-biphenyl)-2-ylmethyl)piperazin1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzenesulfonamide,
or a therapeutically acceptable salt thereof.

11. The compound or therapeutically acceptable salt of claim 1 for use in the treatment of bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound or therapeutically acceptable salt of claim 1 is adapted for administration to a patient in a therapeutically effective amount.

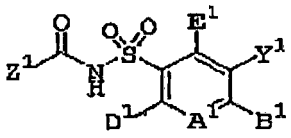
12. The compound or therapeutically acceptable salt for use of claim 11 wherein the compound is N-(4-(4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dmethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzenesulfonamide,

13. The compound or therapeutically acceptable salt for use of claim 11 wherein the compound or therapeutically acceptable salt of claim 1, and one additional therapeutic agent or more than one additional therapeutic agent, are used for treating bladder cancer, brain cancer, breast cancer, bone marrow cancer, cervical cancer, chronic lymphocytic leukemia, colorectal cancer, esophageal cancer, hepatocellular cancer, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, myelogenous leukemia, myeloma, oral cancer, ovarian cancer, non-small cell lung cancer, prostate cancer, small cell lung cancer or spleen cancer in a patient, wherein the compound or therapeutically acceptable salt of claim 1, and the one additional therapeutic agent or the more than one additional therapeutic agent, are adapted for administration to a patient in a therapautically effective amount.

14. The compound or therapeutically acceptable salt for use of claim 13 wherein the compound is N-(4-4-((4'-chloro(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl-propyl)amnio)-3-nitrobenzenesulfonamide.

Patentansprüche

1. Eine Verbindung mit der Formel (I)



(I),

oder ein therapeutisch verträgliches Salz davon, worin

A^1 $C(A^2)$ ist;
A^2 ist H, F, CN, C(O)OH, $C(O)NH_2$ oder $C(O)OCH_3$;
B^1 ist R^1, OR^1, NHR^1, $N(R^1)_2$ oder $NR^1C(O)N(R^1)_2$;
D^1 ist H, F, Cl oder CF_3;
E^1 ist H, F oder Cl;
Y^1 ist H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2, $C(O)NH_2$, oder
B^1 und Y^1 sind, zusammen mit den Atomen, an welche sie gebunden sind, Imidazol oder Triazol;
R^1 ist Phenyl, Pyrolyl, Cyclopentyl, Cyclohexyl, Piperidinyl, Tetrahydrofuranyl, Tetrahydropyranyl, Tetrahydrothiopyranyl oder R^5;
R^5 ist C_1-Alkyl, C_2-Alkyl, C_3-Alkyl, C_4-Alkyl, C_5-Alkyl oder C_6-Alkyl, wobei jedes davon unsubstituiert oder substituiert ist mit einem oder zwei oder drei unabhängig gewählten C_4-Spiroalkyl, C_5-Spiroalkyl, R^7, OR^7, SR^7, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, $NHC(O)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, OH, C(O)OH oder NH_2-Substituenten;
R^7 ist Phenyl, Furanyl, Imidazolyl, Pyridinyl, Tetrazolyl, Thiazolyl, Thienyl, 1,3-Benzoxazolyl, 1,3-Benzodioxolyl, 1,3-Benzothiazol, Cyclopropyl, Cyclobutyl, Cyclohexyl, Azetidinyl, Morpholinyl, Piperazinyl, Piperidinyl, Thiomorpholinyl, Thiomorpholinylsulfon 7-Azabicyclo[2.2.1]heptanyl, 8-Azabicyclo[3.2.1]octanyl, 4,5-Dihydro-1H-imidazolyl 2-Oxa-5-azabicyclo[2.2.1]heptanyl, 1,4,5,6-Tetrahydropyrimidinyl oder R^{11};
R^{11} ist C_1-Alkyl, C_2-Alkyl, C_3-Alkyl oder C_4-Alkyl, wobei jedes davon unsubstituiert oder substituiert ist mit einem oder zwei oder drei unabhängig gewählten R^{12}, OR^{12}, $N(R^{12})_2$, $C(O)N(R^{12})_2$, OH, C(O)OH, NH_2, CF_3, F, Cl, Br oder I Substituenten;
R^{12} ist 1,3-Benzodioxolyl, Pyridinyl, Morpholinyl oder C_1-Alkyl;
Z^1 ist Phenyl oder Pyridinyl, wobei jedes davon substituiert ist mit Cyclohexenyl, Piperazinyl, Piperidinyl, 1,2,3,6-Tetrahydropyridinyl oder Octahydropyrrolo[3,4-c]pyrrolyl, wobei jedes davon substituiert ist mit CH_2R^{37}, $C(C_2$-Spiroalkyl$)(R^{37})$ oder $C(O)R^{37}$;
R^{37} ist Phenyl, Naphthyl, Imidazolyl, Pyrazolyl, Pyridinyl, Cyclopentenyl, Cyclohexenyl, Cycloheptenyl, Cyclooctenyl oder 3,6-Dihydro-2H-pyranyl, wobei jedes davon substituiert ist mit R^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{41}$ oder SR^{41};
R^{41} ist Phenyl, Naphthyl, Cyclohexyl, Morpholinyl, Piperidinyl, Thienyl, Pyridinyl, Chinolinyl, Benzofuranyl, 1,3-Benzodioxolyl, Isoindolinyl, 1,3-Oxazolidin-2-onyl oder R^{45};
R^{45} ist C_1-Alkyl, C_2-Alkyl, C_3-Alkyl oder C_4-Alkyl, wobei jedes davon substituiert ist mit Phenyl;
worin die Anteile, die dargestellt sind durch B^1 und Y^1, zusammen substituiert sind mit C_2-Alkyl, C_3-Alkyl oder C_4-Alkyl, wobei jedes davon substituiert ist mit einem oder zwei unabhängig gewählten SR^{55} oder $N(R^{55})_2$ Substituenten, worin R^{55} unabhängig gewähltes Phenyl oder C_1-Alkyl ist;
die Anteile, die dargestellt sind durch R^1, sind unsubstituiert oder substituiert mit einem oder zwei unabhängig gewählten R^{50}, OR^{50}, SR^{50}, SO_2R^{50}, $CO(O)R^{50}$ oder OCF_3 Substituenten, worin R^{50} Phenyl, C_1-Alkyl, C_2-Alkyl, C_3-Alkyl oder C_4-Alkyl ist;
die Anteile, die dargestellt sind durch R^7, sind unsubstituiert oder substituiert mit einem oder zwei unabhängig gewählten R^{50}, OR^{50}, $C(O)NHSO_2R^{50}$, $CO(O)R^{50}$, $C(O)R^{50}$, C(O)OH, C(O)NHOH, OH, NH_2, F, Cl, Br oder I Substituenten, worin R^{50} Phenyl, Tetrazolyl oder R^{54} ist, worin R^{54} C_1-Alkyl, C_2-Alkyl oder C_3-Alkyl ist, wobei jedes davon unsubstituiert oder substituiert ist mit Phenyl;

die Phenyl- und Pyridinylanteile von Z^1 sind weiter unsubstituiert oder substituiert mit einem oder zwei unabhängig gewählten F, Br, Cl oder I Substituenten;
das Cyclohexenyl, Piperazinyl, Piperidinyl, 1,2,3,6-Tetrahydropyridinyl und Octahydropyrrolo[3,4-c]pyrrolylanteile von Z^1 sind weiter unsubstituiert oder substituiert mit OR^{54}, worin R^{54} C_1-Alkyl oder C_2-Alkyl ist, wobei jedes davon unsubstituiert ist oder substituiert ist mit $N(C_1\text{-Alkyl})_2$, Morpholinyl, Piperidinyl oder Piperidinyl;
die Anteile, die dargestellt sind durch R^{37}, sind weiter unsubstituiert oder substituiert mit einem oder zwei unabhängig gewählten C_1-Alkyl, F, Br, Cl oder I Substituenten; und
die Anteile, die dargestellt sind durch R^{41}, sind unsubstituiert oder substituiert mit einem oder zwei unabhängig gewählten R^{50}, OR^{50}, SR^{50}, $N(R^{50})_2$, SO_2R^{50}, CN, CF_3, F, Cl, Br oder I Substituenten, worin R^{50} Phenyl oder R^{54} ist, worin R^{54} C_1-Alkyl, C_2-Alkyl oder C_3-Alkyl ist, wobei jedes davon unsubstituiert oder substituiert ist mit $N(C_1\text{-Alkyl})_2$ oder Morpholinyl.

2. Eine pharmazeutische Zusammensetzung umfassend Verbindungen gemäß Anspruch 1 oder ihre pharmazeutisch verträglichen Salze.

3. Verbindungen gemäß Anspruch 1 oder ihre pharmazeutisch verträglichen Salze für die Verwendung in der Medizin.

4. Eine Zusammensetzung für die Verwendung in der Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, lymphoiden Malignitäten T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Bronchialkarzinom, Prostatakrebs, kleinzelligem Bronchialkarzinom oder Milzkrebs, wobei die Zusammensetzung einen Hilfsstoff und eine therapeutisch wirksame Menge der Verbindung oder des therapeutisch verträglichen Salzes gemäß Anspruch 1 umfasst.

5. Verwendung einer Verbindung oder eines therapeutisch verträglichen Salzes gemäß Anspruch 1 für die Herstellung eines Medikaments für die Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, lymphoiden Malignitäten T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Bronchialkarzinom, Prostatakrebs, kleinzelligem Bronchialkarzinom oder Milzkrebs in einem Patienten, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 angepasst ist für die Verabreichung an einen Patienten in einer therapeutisch wirksamen Menge.

6. Verwendung gemäß Anspruch 5, worin die Verbindung N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzensulfonamid ist.

7. Verwendung gemäß Anspruch 5, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 und ein zusätzlicher therapeutischer Wirkstoff oder mehr als ein zusätzlicher therapeutischer Wirkstoff verwendet werden für die Herstellung eines Medikaments für die Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, lymphoiden Malignitäten T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Bronchialkarzinom, Prostatakrebs, kleinzelligem Bronchialkarzinom oder Milzkrebs, in einem Patienten, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 und der eine zusätzliche therapeutische Wirkstoff oder die mehr als ein zusätzlichen therapeutischen Wirkstoffe angepasst sind für die Verabreichung an einen Patienten in einer therapeutisch wirksamen Menge.

8. Verwendung gemäß Anspruch 7 worin die Verbindung N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzensulfonamid ist.

9. Die Verbindung gemäß Anspruch 1, worin die Verbindung N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid oder ein therapeutisch verträgliches Salz davon ist.

10. Die Verbindung gemäß Anspruch 1, worin die Verbindung gewählt ist aus:

N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phenylsulfanyl)me-

thyl)-3-(pyrrolidin-1-yl)propyl)amino)benzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(1,3-thiazol-2-ylsulfanyl)ethyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((1,3-thiazol-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((thien-2-ylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-2-(2-(dimethylamino)ethoxy)-1-((phenylsulfanyl)methyl)ethyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-methyl-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(methylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid;
(3R)-3-(4-(((4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-4-(phenylsulfanyl)buttersäure;
(3R)-3-(4-(((4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)amino)sulfonyl)-2-nitroanilino)-N-isopropyl-4-(phenylsulfanyl)butanamid;
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid;
4-(((1R)-3-(Azetidin-1-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((4'-chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzensulfonamid;
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-hydoxy-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
4-(((1R)-3-(Dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((3'-methoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitrobenzensulfonamid,
N-(4-(4-((3'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((2'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
4-(((1R)-3-(Dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-N-(4-(4-((2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperzain-1-yl)benzoyl)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)cyclopentyl)amino)benzensulfonamid,
N-(4-(4-((4'-Fluor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzensulfonamid,
N-(4-(4-((3',4'-Dichlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfanyl)ethyl)amino)benzensulfonamid,
N-(4-(4-((3',4'-Dichlor(1,1'-biphenyl-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((3',4'-Dichlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
3-Nitro-N-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((2-(phenylsulfanyl)ethyl)amino)benzensulfonamid,
4-(((1R)-3-(Morpholin-4-yl)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitro-n-(4-(4-((4'-phenoxy(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)benzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1S)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-((1,1-dimethyl-2-(phenylsulfonyl)ethyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-(2',4'-Dichlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((4'-Chlor-2'-methyl(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((2',4'-Difluor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phe-

nylsulfanyl)methyl)propyl)amino)-3-nitrobenzensulfonamid,
N-(4-(4-((1,1'-Biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzensulfonamid,
N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-3-nitro-4-((2-(phenylsulfonyl)ethyl)amino)benzensulfonamid, und
N-(4-(4-((1,1'-Biphenyl)-2-ylmethyl)piperazin-1-yl)benzoyl)-3-nitro-4-((4-(phenylsulfanyl)tetrahydro-3-furanyl)amino)benzensulfonamid,
oder einem pharmazeutisch verträglichen Salz davon.

11. Die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 für die Verwendung in der Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, lymphoiden Malignitäten T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Bronchialkarzinom, Prostatakrebs, kleinzelligem Bronchialkarzinom oder Milzkrebs in einem Patienten, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1 angepasst ist für die Verabeichung an einen Patienten in einer therapeutisch wirksamen Menge.

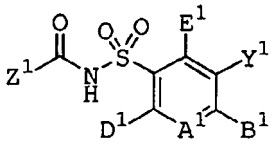
12. Die Verbindung oder das therapeutisch verträgliche Salz für die Verwendung gemäß Anspruch 11, worin die Verbindung N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzensulfonamid ist.

13. Die Verbindung oder das therapeutisch verträgliche Salz für die Verwendung gemäß Anspruch 11, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1, und ein zusätzlicher therapeutischer Wirkstoff oder mehr als ein zusätzlicher therapeutischer Wirkstoff verwendet werden für die Behandlung von Blasenkrebs, Hirntumor, Brustkrebs, Knochenmarkkrebs, Gebärmutterhalskrebs, chronischer lymphatischer Leukämie, Kolorektalkrebs, Speiseröhrenkrebs, Leberzellkrebs, Lymphoblastenleukämie, follikulärem Lymphom, lymphoiden Malignitäten T-Zell- oder B-Zell-Ursprungs, Melanom, myeloischer Leukämie, Myelom, Mundkrebs, Eierstockkrebs, nicht-kleinzelligem Bronchialkarzinom, Prostatakrebs, kleinzelligem Bronchialkarzinom oder Milzkrebs in einem Patienten, worin die Verbindung oder das therapeutisch verträgliche Salz gemäß Anspruch 1, und der zusätzliche therapeutische Wirkstoff oder der mehr als eine zusätzliche therapeutische Wirkstoff, angepasst sind für die Verabreichung an einen Patienten in einer therapeutisch wirksamen Menge.

14. Die Verbindung oder das therapeutisch verträgliche Salz für die Verwendung gemäß Anspruch 13, worin die Verbindung N-(4-(4-((4'-Chlor(1,1'-biphenyl)-2-yl)methyl)piperazin-1-yl)benzoyl)-4-(((1R)-3-(dimethylamino)-1-((phenylsulfanyl)methyl)-propyl)amino)-3-nitrobenzensulfonamid ist.

Revendications

1. Composé ayant la formule (I)



(I),

ou l'un de ses sels thérapeutiquement acceptables, où

A^1 représente $C(A^2)$;
A^2 représente H, F, CN, C(O)OH, $C(O)NH_2$ ou $C(O)OCH_3$;
B^1 représente R^1, OR^1, NHR^1, $N(R^1)_2$ ou $NR^1C(O)N(R^1)_2$;
D^1 représente H, F, Cl ou CF_3 ;
E^1 représente H, F ou Cl ;
Y^1 représente H, CN, NO_2, F, Cl, CF_3, OCF_3, NH_2, $C(O)NH_2$, ou
B^1 et Y^1, conjointement avec les atomes auxquels ils sont fixés, représentent un groupe imidazole ou triazole ;

R^1 représente un groupe phényle, pyrrolyle, cyclopentyle, cyclohexyle, pipéridinyle, tétrahydrofuranyle, tétrahydropyranyle, tétrahydrothiopyranyle ou R^5 ;
R^5 représente un groupe alkyle en C_1, alkyle en C_2, alkyle en C_3, alkyle en C_4 , alkyle en C_5 ou alkyle en C_6, chacun d'eux est non substitué ou substitué par un ou deux ou trois substituants choisis indépendamment spiroalkyle en C_4, spiroalkyle en C_5, R^7, OR^7, SR^7, SO_2R^7, NHR^7, $N(R^7)_2$, $C(O)R^7$, $C(O)NH_2$, $C(O)NHR^7$, $NHC(O)R^7$, $NHSO_2R^7$, $NHC(O)OR^7$, $NHC(O)NH_2$, $NHC(O)CH(CH_3)NHC(O)CH(CH_3)NH_2$, OH, C(O)OH ou NH_2 ;
R^7 représente un groupe phényle, furanyle, imidazolyle, pyridinyle, tétrazolyle, thiazolyle, thiényle, 1,3-benzoxazolyle, 1,3-benzodioxolyle, 1,3-benzothiazole, cyclopropyle, cyclobutyle, cyclohexyle, azétidinyle, morpholinyle, pipérazinyle, pipéridinyle, thiomorpholinyle, thiomorpholinyl-sulfone, 7-azabicyclo[2.2.1]heptanyle, 8-azabicyclo[3.2.1]octanyle, 4,5-dihydro-1H-imidazolyl-2-oxa-5-azabicyclo[2.2.1]heptanyle, 1,4,5,6-tétrahydropyrimidinyle ou R^{11} ;
R^{11} représente un groupe alkyle en C_1, alkyle en C_2, alkyle en C_3 ou alkyle en C_4, chacun d'eux est non substitué ou substitué par un ou deux ou trois substituants choisis indépendamment R^{12}, OR^{12}, $N(R^{12})_2$, $C(O)N(R^{12})_2$, OH, C(O)OH, NH_2, CF_3, F, Cl, Br ou I ;
R^{12} représente un groupe 1,3-benzodioxolyle, pyridinyle, morpholinyle ou alkyle en C_1 ;
Z^1 représente un groupe phényle ou pyridinyle, chacun d'eux est substitué par un groupe cyclohexényle, pipérazinyle, pipéridinyle, 1,2,3,6-tétrahydropyridinyle ou octahydropyrrolo[3,4-c]pyrrolyle, chacun d'eux est substitué par un groupe CH_2R^{37}, C (spiroalkyl en C_2)(R^{37}) ou $C(O)R^{31}$;
R^{37} représente un groupe phényle, naphtyle, imidazolyle, pyrazolyle, pyridinyle, cyclopentényle, cyclohexényle, cycloheptényle, cyclooctényle ou 3,6-dihydro-2H-pyranyle, chacun d'eux est substitué par R^{41}, NHR^{41}, $N(R^{41})_2$, $NHC(O)OR^{91}$ ou SR^{41} ;
R^{41} représente un groupe phényle, naphtyle, cyclohexyle, morpholinyle, pipéridinyle, thiényle, pyridinyle, quinoléinyle, benzofuranyle, 1,3-benzodioxolyle, isoindolinyle, 1,3-oxazolidin-2-onyle ou R^{45} ;
R^{45} représente un groupe alkyle en C_1, alkyle en C_2, alkyle en C_3 ou alkyle en C_4, chacun d'eux est substitué par un groupe phényle ;
où les radicaux représentés par B^1 et Y^1 ensemble sont substitués par un groupe alkyle en C_2, alkyle en C_3 ou alkyle en C_4, chacun d'eux est substitué par un ou deux substituants choisis indépendamment SR^{55} ou $N(R^{55})_2$, où R^{55} est choisi indépendamment parmi un groupe phényle ou alkyle en C_1 ;
les radicaux représentés par R^1 sont non substitués ou substitués par un ou deux substituants choisis indépendamment R^{50}, OR^{50}, SR^{50}, SO_2R^{50}, $CO(O)R^{50}$ ou OCF_3, où R^{50} représente un groupe phényle, alkyle en C_1, alkyle en C_2, alkyle en C_3 ou alkyle en C_4 ;
les radicaux représentés par R^7 sont non substitués ou substitués par un ou deux substituants choisis indépendamment R^{50}, OR^{50}, $C(O)NHSO_2R^{50}$, $CO(O)R^{50}$, $C(O)R^{50}$, C(O)OH, C(O)NHOH, OH, NH_2, F, Cl, Br ou I, où R^{50} représente un groupe phényle, tétrazolyle ou R^{54}, où R^{54} représente un groupe alkyle en C_1, alkyle en C_2 ou alkyle en C_3, chacun d'eux est non substitué ou substitué par un groupe phényle ;
les radicaux phényle et pyridinyle de Z^1 sont en outre non substitués ou substitués par un ou deux substituants choisis indépendamment F, Br, Cl ou I ;
les radicaux cyclohexényle, pipérazinyle, pipéridinyle, 1,2,3,6-tétrahydropyridinyle et octahydropyrrolo[3,4-c]-pyrrolyle de Z^1 sont en outre non substitués ou substitués par OR^{59}, où R^{59} représente un groupe alkyle en C_1 ou alkyle en C_2, chacun d'eux est non substitué ou substitué par un groupe N(alkyle en $C_1)_2$, morpholinyle, pipéridinyle ou pipéridinyle ;
les radicaux représentés par R^{37} sont en outre non substitués ou substitués par un ou deux substituants choisis indépendamment alkyle en C_1, F, Br, Cl ou I ; et
les radicaux représentés par R^{41} sont non substitués ou substitués par un ou deux substituants choisis indépendamment R^{50}, OR^{50}, SR^{50}, $N(R^{50})_2$, SO_2R^{50}, CN, CF_3, F, Cl, Br ou I, où R^{50} représente un groupe phényle ou R^{54}, où R^{54} représente un groupe alkyle en C_1, alkyle en C_2 ou alkyle en C_3, chacun d'eux est non substitué ou substitué par un groupe N (alkyle en $C_1)_2$ ou morpholinyle.

2. Composition pharmaceutique comprenant des composés selon la revendication 1 ou leurs sels pharmaceutiquement acceptables.

3. Composés selon la revendication 1 ou leurs sels pharmaceutiquement acceptables pour une utilisation en médecine.

4. Composition pour une utilisation dans le traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatocellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, des affections malignes lymphoïdes ayant pour origine les lymphocytes T ou les lymphocytes B, du

mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate, ladite composition comprenant un excipient et une quantité thérapeutiquement efficace du composé ou de l'un de ses sels thérapeutiquement acceptables selon la revendication 1.

5. Utilisation d'un composé ou de l'un de ses sels thérapeutiquement acceptables selon la revendication 1 pour la fabrication d'un médicament destiné au traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatocellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, des affections malignes lymphoïdes ayant pour origine les lymphocytes T ou les lymphocytes B, du mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate chez un patient, où le composé ou l'un de ses sels thérapeutiquement acceptables selon la revendication 1 est adapté pour une administration à un patient dans une quantité thérapeutiquement efficace.

6. Utilisation selon la revendication 5, où le composé est le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide.

7. Utilisation selon la revendication 5, où le composé ou l'un de ses sels thérapeutiquement efficaces selon la revendication 1, et un agent thérapeutique supplémentaire ou plus d'un agent thérapeutique supplémentaire, sont employés pour fabriquer un médicament destiné au traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatocellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, des affections malignes lymphoïdes ayant pour origine les lymphocytes T ou les lymphocytes B, du mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate chez un patient, où le composé ou l'un de ses sels thérapeutiquement efficaces selon la revendication 1, et l'agent thérapeutique supplémentaire ou le plus d'un agent thérapeutique supplémentaire, sont adaptés pour une administration à un patient dans une quantité thérapeutiquement efficace.

8. Utilisation selon la revendication 7, où le composé est le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phényl-sulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide.

9. Composé selon la revendication 1 ou le composé est le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-y1)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)-méthyl)propyl)amino)-3-nitrobenzènesulfonamide ou l'un de ses sels thérapeutiquement acceptables.

10. Composé selon la revendication 1, où le composé est choisi parmi :

le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-(((1R)-1-((phénylsulfanyl)méthyl)-3-(pyrrolidin-1-yl)propyl)amino)-benzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-((1,1-diméthyl-2-(1,3-thiazol-2-yl-sulfanyl)éthyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((1,3-thiazol-2-ylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((thién-2-ylsulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-2-(2-(diméthylamino)éthoxy)-1-((phénylsulfanyl)méthyl)éthyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-l-yl)benzoyl)-4-(((1S)-3-(diméthylamino)-1-méthyl-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(méthylamino)-1-((phényl-sulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide,
l'acide (3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)amino)sulfonyl)-2-nitro-anilino)-4-((phénylsulfanyl)butanoïque,
le (3R)-3-(4-(((4-(4-((4'-chloro(1,1'-biphényl)-2-yl)-méthyl)pipérazin-1-yl)benzoyl)amino)sulfonyl)-2-nitro-anilino)-N-isopropyl-4-((phénylsulfanyl)butanamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diisopropylamino)-

1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le 4-(((1R)-3-(azétidin-1-yl)-1-((phénylsulfanyl)-méthyl)propyl)amino)-N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-((4-(phénylsulfanyl)-tétrahydro-3-furanyl)amino)benzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-hydroxy-1-((phényl-sulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(isopropylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le 4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)-méthyl)propyl)amino)-N-(4-(4-((3'-méthoxy(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)-3-nitrobenzènesulfonamide,
le N-(4-(4-((3'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((2'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le 4-((((1R)-3-(diméthylamino)-1-((phénylsulfanyl)-méthyl)propyl)amino)-N-(4-(4-((2'-méthyl(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-((2-(phénylsulfanyl)-cyclopentyl)amino)benzènesulfonamide,
le N-(4-(4-((4'-fluoro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-((2-(phénylsulfanyl)éthyl)-amino)benzènesulfonamide,
le N-(4-(4-((3',4'-dichloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-((2-(phénylsulfanyl)éthyl)-amino)benzènesulfonamide,
le N-(4-(4-((3',4'-dichloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phényl-sulfanyl)méthyl).propyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((3',4'-dichloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(morpholin-4-yl)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le 3-nitro-N-(4-(4-((4'-phénoxy(1,1'-biphényl)-2-yl)-méthyl)-pipérazin-1-yl)benzoyl)-4-((2-(phénylsulfanyl)éthyl)-amino)benzènesulfonamide,
le 4-(((1R)-3-(morpholin-4-yl)-1-((phénylsulfanyl)-méthyl)propyl)amino)-3-nitro-N-(4-(4-((4'-phénoxy(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)benzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1S)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-((1,1-diméthyl-2-(phénylsulfonyl)-éthyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((2',4'-dichloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phényl-sulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((4'-chloro-2'-méthyl(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide,
le N-(4-(4-((2',4'-difluoro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phényl-sulfanyl)méthyl)propyl)amino)-3-nitrobenzènesulfonamide,
le N-(4-(4-((1,1'-biphényl)-2-ylméthyl)-pipérazin-1-yl)-benzoyl)-3-nitro-4-((2-(phénylsulfonyl)éthyl)amino)benzène-sulfonamide,
le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)-pipérazin-1-yl)benzoyl)-3-nitro-4-((2-(phénylsulfonyl)éthyl)-amino)benzènesulfonamide, et
le N-(4-(4-((1,1'-biphényl)-2-ylméthyl)-pipérazin-1-yl)-benzoyl)-3-nitro-4-((4-(phénylsulfanyl)tétrahydro-3-furanyl)-amino)benzènesulfonamide,
ou l'un de leurs sels thérapeutiquement acceptables.

11. Composé ou l'un de ses sels thérapeutiquement acceptables selon la revendication 1, pour une utilisation dans le traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatocellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, des affections malignes lymphoïdes ayant pour origine les lymphocytes T ou les lymphocytes B, du mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate chez un patient, où le composé ou l'un de ses sels thérapeutiquement acceptables selon la revendication 1 est adapté pour une administration à un patient dans une quantité thérapeutiquement efficace.

12. Composé ou l'un de ses sels thérapeutiquement acceptables pour une utilisation selon la revendication 11, où le composé est le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)méthyl)pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide.

13. Composé ou l'un de ses sels thérapeutiquement acceptables pour une utilisation selon la revendication 11, où le composé ou l'un de ses sels thérapeutiquement acceptables selon la revendication 1, et un agent thérapeutique supplémentaire ou plus d'un agent thérapeutique supplémentaire, sont utilisés pour le traitement du cancer de la vessie, du cancer du cerveau, du cancer du sein, du cancer de la moelle osseuse, du cancer du col de l'utérus, de la leucémie lymphocytaire chronique, du cancer colorectal, du cancer oesophagien, du cancer hépatocellulaire, de la leucémie lymphoblastique, du lymphome folliculaire, des affections malignes lymphoïdes ayant pour origine les lymphocytes T ou les lymphocytes B, du mélanome, de la leucémie myélogène, du myélome, du cancer buccal, du cancer ovarien, du cancer du poumon non à petites cellules, du cancer de la prostate, du cancer du poumon à petites cellules ou du cancer de la rate chez un patient, où le composé ou l'un de ses sels thérapeutiquement acceptables selon la revendication 1, et l'agent thérapeutique supplémentaire ou le plus d'un agent thérapeutique supplémentaire, sont adaptés pour une administration à un patient dans une quantité thérapeutiquement efficace.

14. Composé ou l'un de ses sels thérapeutiquement acceptables pour une utilisation selon la revendication 13, où le composé est le N-(4-(4-((4'-chloro(1,1'-biphényl)-2-yl)-méthyl)pipérazin-1-yl)benzoyl)-4-(((1R)-3-(diméthylamino)-1-((phénylsulfanyl)méthyl)propyl)amino)-3-nitrobenzène-sulfonamide.

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